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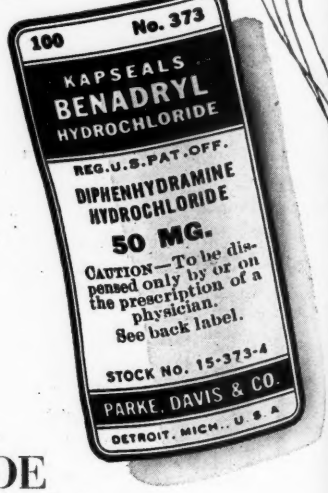

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EPIDEMIC-TYPHUS ANTIBODIES IN HUMAN SUBJECTS IN BOSTON, MASSACHUSETTS*

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BOSTON

When a clinician is consulted by a patient who formerly lived in an epidemic typhus zone and who now has fever, headache and possibly a rash, he must include Brill's disease in his differential diagnosis.[1, 2] The confirmation or elimination of the diagnosis of Brill's disease depends on the use of the complement-fixation test with epidemic typhus antigen.[1, 3]

The interpretation of the results of the complement-fixation test is influenced by Zinsser's concept,[4] which postulates that a patient with Brill's disease has previously suffered an attack of louse-borne typhus fever. This hypothesis has been considerably strengthened by recent studies.[1-3] Anyone suspected of having Brill's disease, as well as other persons from the foreign-born group of which he is a member, might logically be expected to have residual epidemic-typhus antibodies, since it is well known that epidemic-typhus antibodies may be demonstrated for at least two or three years after an acute attack of the disease.[5] However, the incidence and magnitude of antibody titers to epidemic typhus in immigrants from the typhus zones of Europe have not been adequately investigated.

This paper presents data on antibodies to epidemic typhus found in serums obtained from 519 American and foreign-born persons now residents of the metropolitan area of Boston.

Composition of Study Groups

In view of the fact that increasingly sensitive tests were evolved as our study progressed, the serums are considered in two groups. Most of the subjects were patients in the Beth Israel Hospital.

Group I consisted of serums drawn from 419 unselected American and foreign-born patients. It was subdivided into Group IA, serums from 222 patients born in typhus areas, and Group IB, serums from 197 patients born in the United States or Canada.

Group II consisted of 100 serums tested by more sensitive serologic technics developed during our earlier studies.[6] It was subdivided into Group IIA, serums from 50 foreign-born patients (immigrants to the United States from typhus zones of Russia, Latvia, Lithuania, Poland and Rumania) and Group IIB, serums from 50 patients born in the United States or Canada; two thirds of the patients in Group IIB were admitted to the Haynes Memorial Hospital.

No person was included in this study if he had been outside the United States since 1940 or if he had ever received epidemic-typhus or any other rickettsial vaccine. The patients were admitted to the hospital for various conditions, including surgical and metabolic disorders. A small proportion of the patients with positive titers had fevers, but in each case the cause of the fever was clearly established and could not be ascribed to rickettsial infection.

Serologic Technics

Group I serums were all obtained from routine admission blood specimens and were stored at 5°C. Group II serums were separated from specimens of blood taken specifically for this study. The blood was drawn into vacuum tubes and kept overnight at 5°C.; the serums were subsequently stored at −20°C. until tested.

Complement-Fixation Tests

Group I serums were tested by the method used in the Army Medical Department Research and Graduate School,[7] as modified by use of a magnesium buffer solution[8] instead of saline as the diluent. The antigen was a suspension of killed washed epidemic-typhus rickettsiae.*

*From the Beth Israel Hospital, Boston, and the Department of Microbiology, Harvard School of Public Health.

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Group II serums were tested by modified complement-fixation methods developed during the study of Group I serums. These modifications enhanced both sensitivity and specificity. One change consisted in the use of "soluble antigen" derived from epidemic-typhus rickettsiae,[9] which frequently resulted in titers two- to fourfold higher than those obtained with the antigen used for Group I serums. The other modification was the inactivation of serums at 59.5°C. rather than at 56°C., a change that eliminated the occasionally troublesome prozone reactions. The validity of the technics applied to antibodies; the test was used simply to establish the presence or absence of typhus antibodies as a check on the results of the complement-fixation test.

Results

Group IA

These were serums from 222 foreign-born patients from typhus areas of Europe (preliminary screening technic). Thirty-one patients were shown to have antibodies to epidemic typhus; the serums of 191 were negative. The positive serums were later subjected to the mouse-toxin neutralization test; all were found to have antibodies that protected mice against two certainly fatal toxic doses of epidemic typhus rickettsiae (Table 1).

Table 1. *Data on Group I (31 Boston Residents Born in European Typhus Zones Who Had Epidemic-Typhus Antibodies).**

Case No.	Age	Sex	Birthplace	Approximate Year of Arrival in the United States	Denominator of Complement-Fixation Titers		Mouse-Toxin Neutralization Test
					Epidemic typhus	Murine typhus	*ratio: survivors to total number inoculated*
C-25	68	F	Latvia	1895	10	0	2/2
C-85	73	M	Russia	1900	10	0	2/2
C-176	80	M	Russia	1889	10	−	2/2
C-342	67	F	Russia	1901	10	−	3/3
C-388	75	F	Russia	1935	10	0	4/4
C-509	54	F	Russia	1906	10	0	8/8
C-512	73	M	Russia	1905	10	0	6/7
C-603	82	M	Russia	1910	10	0	4/4
C-708	57	M	Russia	1908	10	0	13/13
C-734	77	M	Russia	1920	10	0	4/4
C-318	68	F	Russia	1900	10+	±	4/4
C-528	68	M	Russia	1901	10+	−	2/2
C-667	73	M	Russia	1909	10+	−	1/1
C-47	78	F	Lithuania	1903	20	0	2/2
C-90	68	M	Russia	1900	20	0	2/2
C-108	57	M	Russia	1908	20	0	2/2
C-168	75	M	Russia	1903	20	−	2/2
C-517	58	F	Russia	1914	20	0	4/4
C-578	58	F	Russia	1906	20	0	3/3
C-583	86	M	Russia	1886	20	0	8/8
C-657	62	F	Russia	1908	20	0	8/8
C-663	60	M	Russia	1904	20	0	4/4
C-718	70	F	Russia	1907	20	0	2/2
C-240	74	M	Russia	1903	40	10	4/4
C-370	67	M	Russia	1914	40	±	4/4
C-1	57	M	Russia	1905	80	20	4/4
C-21	67	M	Russia	1892	80	10	2/2
C-56	73	F	Russia	1920	80	±	1/1
C-144	66	M	Russia	1901	80	±	1/1
C-55	66	M	Russia	1893	160	20	2/2
C-660	51	M	Russia	1922	160	20+	2/2

*In addition to the 31 patients listed in this table, there were 191 additional patients in Group IA and 197 patients in Group IB whose serums were all negative in the complement-fixation test and hence are not tabulated.

Group IB

These were serums from 197 patients born in the United States or Canada (preliminary screening technic). These specimens were negative.

Group IIA

These were serums from 50 foreign-born patients (tested by modified complement-fixation and neutralization tests). Seventeen patients had positive complement-fixation tests in serum dilutions ranging from 1/5 to 1/320 with a geometric mean titer of 1/24.5. The same serums also gave complete protection to mice against two certainly fatal toxic

Group II serums was checked by parallel tests using the mouse-toxin neutralization test.

Neutralization Tests

The positive serums in Group I and all the serums in Group II were tested for mouse-toxin neutralizing antibodies. The technic was essentially that described by Henderson[10]; the serum was mixed and incubated at 5°C. with a suspension of living epidemic typhus rickettsiae titrated to contain two certainly fatal toxic doses in final concentration. Mice that receive such a mixture survive only when typhus antibodies are present in the test serum. The high specificity and sensitivity of this mouse-toxin neutralization test for detecting typhus antibodies have been amply demonstrated.[6, 7, 10, 11] No attempt was made to determine the final titers of the neutralizing

doses of epidemic-typhus rickettsiae in the mouse-toxin neutralization test. The only exception was serum F-10, which protected only 3 out of 5 mice tested. The serums of 3 additional patients were negative (at a 1/5 dilution) in the complement-fixation test but gave partial protection to mice in the neutralization test (one serum protected 8 out of 10, a second protected 5 out of 8, and a third protected 2 out of the 4 mice inoculated). These latter 3 serums were considered probably positive for evidence of residual antibodies to epidemic typhus.

The serums of 4 patients were negative (at a 1/5 dilution) in the complement-fixation test. In the neutralization test an occasional mouse survived. These 4 cases are considered probably negative for evidence of residual antibodies to epidemic typhus.

The serums of 26 patients were negative at a 1/5 dilution in the complement-fixation test and also failed to protect mice in the neutralization test. A total of 122 mice were inoculated; there were no survivors. Table 2 shows the data from Group IIA.

TABLE 2. *Data on Group II (20 Boston Residents Born in European Typhus Zones Who Had Epidemic-Typhus Antibodies).**

Case No.	Age	Sex	Birthplace	Approximate Year of Arrival in the United States	Denominator of Complement-Fixation Titers		Mouse-Toxin Neutralization Test
					Epidemic typhus	Murine typhus	*ratio: survivors to total number inoculated*
F-19	70	F	Russia	1902	5	—	6/6
F-2	74	M	Russia	1898	10	—	6/6
F-3	66	M	Russia	1900	10	—	8/8
F-5	75	M	Russia	1901	10	—	6/6
F-25	81	M	Russia	1940	10	—	8/8
F-40	70	M	Russia	1890	10	—	16/16
F-43	79	M	Russia	1938	10	—	8/8
F-48	60	M	Russia	1911	10	—	4/4
F-7	81	M	Russia	1900	20	±	8/8
F-32	70	M	Russia	1933	20	—	4/4
F-49	82	M	Russia	1906	20	10	2/2
F-33	76	F	Russia	1923	40	—	4/4
F-26	48	M	Russia	1920	80	5	8/8
F-50	66	M	Russia	1922	80	10	2/2
F-4	85	M	Poland	1909	160	20	7/7
F-36	60	M	Russia	1910	320	40	12/12
F-9	73	M	Russia	1905	0	0	8/10
F-16	65	M	Russia	1889	0	0	2/4
F-35	61	M	Russia	1914	0	0	5/8
F-10	68	F	Russia	1940	80	0	3/5

*In addition to these 20 positive serums, there were 4 serums that were negative in complement-fixation tests, but a total of 4 mice (1 for each serum) survived out of a total of 38 mice inoculated in the mouse-toxin neutralization test; these serums are considered negative. Twenty-six other serums in Group II A were negative in both complement-fixation and mouse-toxin neutralization tests (total 0/122).

All 50 serums in Group II B were negative in both the complement-fixation and mouse-neutralization tests.

Group IIB

These were serums from 50 patients born in the United States or Canada. The patients had negative complement-fixation tests at a serum dilution of 1/5 and also negative mouse-toxin neutralization tests (Table 3).

TABLE 3. *Summary of Data from Group IIB.*

No. of patients	50
Age range	1½–80 years
Average age	35
Males	28
Females	22
Results of complement-fixation tests	All 50 negative
Results of mouse-toxin neutralization tests	All 50 negative (0/322)*

*Ratio of survivors to total number inoculated.

Summary of Findings on 51 Patients with Positive Serums

For purposes of analysis the data from the 31 patients with positive serologic tests in Group IA and the 20 with positive serologic tests in Group IIA are considered together. Thus, there were 51 immigrants to the United States from typhus zones whose serums had complement-fixing or neutralizing antibodies, or both, to epidemic typhus.

Epidemiologic Data

The 51 patients ranged in age from forty-eight to eighty-six, with an average age of 69.5 years; 37 were men, 14 women; 48 were born in Russia; 1 each was born in Poland, Latvia and Lithuania.

For the 46 patients from whom we obtained fairly accurate information, the period of continuous residence in the United States ranged from twenty-seven to sixty-four years, with the average between forty and fifty years. Thirty-one of the 51 were questioned about whether they recalled a previous attack of typhus; only 5 could recall a specific illness that might have been typhus.

Serologic Data

Forty-seven of the 51 patients had unequivocal evidence of epidemic-typhus antibodies by both

complement-fixation and mouse-toxin neutralization tests. The range of values is indicated in Table 4.

Of the 4 patients with irregular or doubtful complement-fixation or mouse-toxin neutralization results, or both, 1 had a complement-fixing antibody titer of 1/80 but only partial (8/10) protection in the mouse-toxin neutralization test. The 3 remaining subjects had negative complement-fixing titers at a 1/5 dilution with partial (2/4, 3/5 and 5/8) protection in the mouse-toxin neutralization tests.

Murine-typhus antibodies were demonstrated in some serums; in every such instance, however, the epidemic-typhus antibody titers were from two- to sixteenfold higher.

TABLE 4. *Epidemic-Typhus Antibody Titers of 51 Residents of Boston Who Were Born in Typhus Zones of Europe.*

TITERS IN COMPLEMENT-FIXATION TEST USING EPIDEMIC ANTIGEN	NUMBER OF SUBJECTS
0 or ±	3
1/5	1
1/10	17
1/10+	3
1/20	13
1/40	3
1/80	7
1/160	3
1/320	1
Total	51

DISCUSSION

There was a striking difference between the epidemic-typhus antibody titers of subjects born in North America, on the one hand, and those of patients born in the typhus areas of eastern Europe, on the other. The preliminary screening showed that the serums of 197 patients born in North America were negative whereas the serums of 31 of 222 immigrants were positive.

With our modified complement-fixation test combined with the neutralization test, the results were even more striking; all the serums of 50 North-American-born subjects were negative, whereas those of 20 of 50 immigrants were positive.

The actual incidence of prior contact with epidemic-typhus rickettsiae among immigrants from typhus areas may be even higher than indicated in this study. In another paper[9] we describe the residual antibody titers found in 21 American veterans who had documentary evidence of having received their last injection of epidemic-typhus vaccine 3.2 to 8.2 years previously; 8 of these men failed to show any evidence of complement-fixing antibodies even when their undiluted serum was tested; 5 also had no protective antibodies in the mouse-toxin neutralization test. However, all 21 responded promptly to a single injection of epidemic-typhus vaccine by developing relatively high complement-fixing antibody titers by the tenth post-booster day. Such rapid appearance of high antibody titers has been obtained only in those who have had prior contact with living or dead typhus rickettsiae.[6,9] It is possible, therefore, that some of the foreign-born patients whose serums were negative when tested by the more sensitive serologic methods employed in the second part of this study might give a positive response when treated with the vaccine-response technic. Studies of this possibility are in progress.

The height of the antibody titers in the 51 positive serums was surprising. Twenty-seven (52 per cent) of the titers were 1/20 or higher. Of particular interest are the 11 serums with titers of 1/80 to 1/320. It is known that the titer of complement-fixing antibodies has usually fallen below 1/80 two years after a primary attack of louse-borne typhus,[5] and it would be expected that the titer would continue to fall after the second year — or at least not to rise again to such relatively high titers as 1/80 to 1/320. To explain such high titers one might postulate an unrecognized attack of Brill's disease (a recrudescence of the original epidemic-typhus illness) within the two years preceding our study. On the other hand, one might postulate that some other illness, — perhaps some other rickettsial disease, — may have caused an anamnestic rise in the antibody titer. There is evidence against this latter hypothesis in the study of a Q-fever outbreak in a Bosnian village,[12] where most of the persons studied were found to have residual antibodies to epidemic typhus but no anamnestic rise in epidemic-typhus antibodies occurred in association with an acute attack of Q fever.

In any case, the occurrence of such high residual titers as 1/80 to 1/320 in a random population of foreign-born persons makes it necessary to be exceedingly cautious in diagnosing an acute attack of Brill's disease from a single serum specimen with a serum titer of 1/80 to 1/320 or even 1/640. Only with evidence of a rising titer or titers of 1/1000 or greater can one believe that the serologic results are of diagnostic validity.

The significance of low titers (1/10 or less) in the complement-fixation test may be open to question; therefore it is important to note that in this study all complement-fixation titers of 1/10 or lower were confirmed by a positive mouse-toxin neutralization test. Moreover, we have demonstrated elsewhere[6, 9] that patients with low titers in the complement-fixation test respond to a booster dose of typhus vaccine with an antibody pattern similar to that observed in previously immunized patients. These results add further to the evidence that the low complement-fixation titers such as 1/5 or 1/10 that were obtained in these studies indicate the presence of specific antibodies to epidemic-typhus rickettsiae.

One may be surprised that so few of the patients with antibodies to epidemic typhus gave a history suggestive of an acute attack of typhus fever at any time in the past. However, contrary response was obtained in another study recently made of 26 cases of Brill's disease in Yugoslavia, where 21 of the 26 patients could clearly recall an attack of typhus seven to twelve years previously.[3] Again, in a survey[6] made in 1951 of a random sample of serums from a village in Bosnia, Yugoslavia, which had been swept several times by epidemic typhus from 1942 to 1945 during guerrilla warfare, 35 of 43 adults were found to have complement-fixing antibodies to epidemic typhus; 27 of these 35 with residual complement-fixing antibodies stated that they recalled an attack of epidemic typhus seven to ten years previously. Evidently the duration of time between the illness and the time of questioning may be a large factor in determining the kind of answer elicited. Epidemiologic studies on the common communicable diseases in the United States[13] and on yaws in Jamaica[14] also show an inverse relation between age periods and the percentage of persons who can recall having had an attack of the disease in question.

Summary

The serums of 51 immigrants to the United States from typhus zones of Europe were shown to have antibodies to epidemic-typhus rickettsiae by complement-fixation and mouse-toxin neutralization tests. Eleven to sixty-four years had elapsed since these subjects had arrived in the United States.

The combined use of our modified complement-fixation test and the mouse-toxin neutralization test indicated that *at least one third* of a series of 50 immigrants to the United States from typhus zones of Europe had residual typhus antibodies. The same tests, applied to a comparable series of subjects born in the United States or Canada, showed uniformly negative results.

In view of the high incidence of residual typhus antibodies in subjects who have lived in typhus zones, a single positive complement-fixation titer with epidemic-typhus antigen cannot be accepted as diagnostic of Brill's disease even though it may be moderately high. Our findings emphasize the importance of demonstrating rapidly rising titers in serial specimens for the positive diagnosis of Brill's disease.

The authors wish to express appreciation to Dr. Louis Weinstein for furnishing serums from the Haynes Memorial Hospital and to Mrs. Doris Simon and Mr. Peter Skaliy for their assistance in the neutralization tests.

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ELASTIC STOCKINGS IN THE PREVENTION OF PULMONARY EMBOLISM: A PRELIMINARY REPORT*

ROBERT W. WILKINS, M.D.,† GEORGE MIXTER, JR., M.D.,‡ JOSEPH R. STANTON, M.D.,§ AND JULIUS LITTER, M.D.¶

BOSTON

IT IS now generally recognized that pulmonary embolism most commonly arises from clinically silent phlebothrombosis in the deep veins of the leg.[1-4] In their classic paper on this subject, Hunter and his co-workers[4] state: "We are of the opinion that the greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person without the benefit of active exercise or the aid of gravity in the maintenance of an efficient venous circulation."

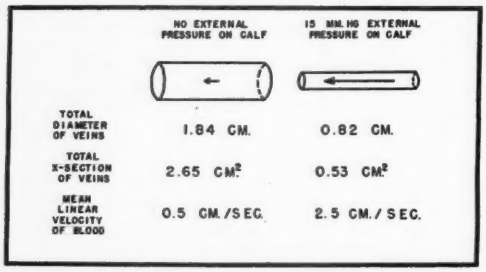

FIGURE 1. *The Effects of 15 mm. Hg. External Pressure on the Leg of a Normal Supine Subject.*

This would reduce the effective (internal minus external) venous pressure to barely greater than zero, the venous volume from 3.0 cc. to 0.6 cc. per 100 cc. of leg[7] and the total cross-sectional area of the veins from 2.65 to 0.53 sq. cm. As a result the mean linear velocity of blood flow (indicated by the length of the arrow) would increase fivefold. The data given in the figure were calculated as if the total volume of the leg veins were contained in a single cylindrical tube. The blood flow (including the venous return from the foot) was assumed to be a normal value of 5.3 cc. per 100 cc. of leg per minute.

Recently radiologic and anatomic studies in this laboratory have demonstrated that aneurysmal enlargements and saccular dilatations often occur in the deep venous system of the calf, particularly in older persons.[5, 6] Collateral physiologic studies have shown that external pressure of 10 to 15 mm. of mercury applied to the leg of a supine person markedly decreases the volume of the limb, presumably by reducing the effective intravascular pressure and hence the volume of the veins[7] (Fig. 1). Separate studies of the linear velocity of blood flow in the veins of the leg during such local compression have shown the flow to be accelerated as compared with control measurements.[5] The explanation offered was that the local compression so reduced the cross-sectional area of the veins that the mean linear velocity of blood flow (being inversely proportional to the cross-sectional area) was increased (Fig. 1). It was interesting to observe that in older persons with dilated deep veins the acceleration of venous flow during local compression was particularly great.

Because of these observations and the generally accepted belief that acceleration of flow would tend to decrease the likelihood of thrombosis in the calf veins, it was decided to try elastic compression of the legs as a prophylactic measure against phlebothrombosis and pulmonary embolism in hospitalized persons. This decision was supported by the additional consideration that even if elastic compression did not completely prevent phlebothrombosis in the legs it might cause such thrombi as did form to be smaller and hence would decrease the likelihood of fatal pulmonary embolism. Accordingly, an alternate-case study of hospitalized patients was instituted to determine the effect of wearing elastic stockings on the incidence of pulmonary embolism. Elastic stockings were chosen rather than elastic leg bandages because preliminary observation had shown the former to be more easily and uniformly applied at correct pressures, with less danger of local garter effects.

METHODS

Only patients over twenty years of age were the subjects of the present investigation. Since each patient on entering this hospital is assigned an admission number at random, the last integer of this number was used. If this integer was even, the patient was placed in the "stocking group"; if it was odd, the patient was enrolled in the "control group." No other factor was considered in assigning a patient to either group. Patients in the control group wore a loosely applied nonelastic stockinette that although affording no significant compression did provide as nearly as possible an equal amount of warmth and elicited the same degree of attention as the elastic stockings worn by the patients in the "stocking group."

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Initially only patients on the open medical and surgical wards were the subjects of the study, but later, as experience and confidence were gained, patients on the other wards were included, until finally all admissions, both ward and private, were made available to the study. Thus, although in a strict sense this was not a study of all consecutive admissions to the hospital it was a study of all admissions consecutively available. One and later two full-time graduate nurses were assigned to follow the patients on the study. It was their duty to measure the legs and apply the proper covering (whether elastic stockings or nonelastic stockinette) and to record on a data sheet a number of factors presumed to be of importance in the development of thromboembolic disease. These sheets were so arranged that the data could be readily transferred to punch cards for statistical analysis. In this manner a large body of information was gathered, much of which, although valuable, is not of immediate concern to this report.

If the question of thromboembolic disease was raised at any time during the patient's stay in the hospital, the patient was seen by one or more of the four physicians assigned to the study and a clinical evaluation was made. Treatment, including the use of anticoagulants, was occasionally discussed, but in each case the handling of the patient was left completely to the regular physician in charge. Except for the wearing of elastic stockings or nonelastic stockinette, the clinical management of the two groups was not known to be affected.

Because of the necessity, in this initial study, of avoiding any possible ill effect from the use of elastic stockings, the wearing of all leg covering by a patient was omitted when either the physician in charge or the physicians assigned to the study thought that the wearing of elastic stockings might possibly be deleterious to the patient. For example, early in the study one patient with severe congestive heart failure, renal insufficiency and peripheral edema developed pulmonary edema soon after the application of elastic stockings. It was therefore ruled that thenceforth in the study patients with significant peripheral edema due to congestive heart failure would be "out of series," whether assigned to the stocking or to the control group. Such patients were still followed in the "out of series" group with the same careful collection of data as those "in series." Likewise, the presence of local ulceration or inflammatory lesions on the leg, the finding of arterial insufficiency, the prescription of other leg coverings such as casts or elastic bandages by the patient's physician or, rarely, a patient's refusal to co-operate was an additional cause for ruling a patient "out of series." Thus, any patient who failed to wear his assigned leg covering for as long as twenty-four hours was ruled "out of series." In all, 12.6 per cent of patients were so classified. It should be emphasized, however, that this figure was probably unduly large because of the decision in this initial trial to omit the wearing of elastic stockings in all patients when they might possibly have done harm.

Two types of analysis were made of the cases included in the study. The first was an evaluation based on all the clinical factors at the disposal of the group, including careful history and elicitation of symptomatology, physical examination and laboratory studies (roentgenographic, electrocardiographic and hematologic). Any patient suspected of possibly having thromboembolic disease, indicated, for example, by an increase in calf size, unexplained rise in temperature or pulse, the appearance of local tenderness, positive Homans' sign, pain or suggestive x-ray findings, became the subject of a consultation and classification by the professional group assigned to the study. The following clinical classifications were used: fatal pulmonary embolism, thromboembolic disease with nonfatal pulmonary embolism, probable thrombotic disease without pulmonary embolism, possible thrombotic disease and no evidence of thrombotic disease.

An analysis was made independently of the postmortem findings on the patients who died in either group. In addition to the routine autopsy procedures, special gross and microscopical examinations were made when possible in questionable or suspicious cases to establish whether or not ante-mortem thromboembolic disease had been present. Due to a variety of factors, however, complete dissection of the leg veins was not routinely carried out. The autopsied cases were then diagnosed as follows: fatal pulmonary embolism, thromboembolic disease with nonfatal pulmonary embolism, thrombotic disease without pulmonary embolism and no evidence of thrombotic disease.

Results

Analysis of Clinical Data

Exactly half of the 5426 consecutively available patients were assigned by chance to wear elastic stockings and half to wear loosely applied nonelastic stockinette. Of patients assigned to the elastic-stocking group, 367, for one of the reasons mentioned above, did not wear the stockings continuously during their hospital stay and were classified as "out of series." Among the 2346 acceptable patients remaining "in series" in the stocking group, there were no deaths from pulmonary embolism.

In the control group, 318 patients did not wear the control stockinette (or, had they chanced to fall in the stocking group, could not have worn elastic stockings) and were therefore ruled "out of series." Of the remaining 2395 "in series" control patients who did wear nonelastic stockinette throughout their hospital stay there were 4 deaths from pulmonary embolism; 2 were confirmed at

autopsy and the other 2 were diagnosed clinically by all the attending physicians concerned. Three of these 4 deaths occurred in surgical patients after operation; the fourth was in a medical patient with severe mitral stenosis but without significant peripheral edema. In addition, among the "in series" control patients 12 were diagnosed clinically as having nonfatal pulmonary embolism (4 confirmed at autopsy), and among the "in series" elastic-stocking patients there were 2 such cases (1 confirmed at autopsy). On the basis of local symptoms and signs in the legs, 9 patients in the control group and 13 patients in the stocking group were diagnosed as having probable thrombotic disease without pulmonary embolism; 18 and 20 respectively were diagnosed as having possible thrombotic disease without pulmonary embolism (Table 3).

Analysis of Autopsy Data

In a disease as difficult to diagnose clinically as thromboembolism one can be certain of the diagnosis only at the autopsy table. Therefore, particular stress was laid on the post-mortem studies. Among the "in series" cases there were 100 deaths from all causes in the stocking group and 89 in the control group, with 64 (64 per cent) and 51 (57.3 per cent) autopsies respectively. In cases with embolism proved at autopsy, decision had to be made concerning whether the embolism was the chief cause of death ("fatal") or only contributory ("nonfatal"). In doubtful cases the diagnosis of "nonfatal pulmonary embolism" was made. The autopsy diagnoses with respect to thromboembolic disease were as follows:

TABLE 1. *Post-Mortem Diagnoses in Deaths in Stocking and Control Groups.*

AUTOPSY DIAGNOSES	STOCKING GROUP	CONTROL GROUP
Fatal pulmonary embolism	0	2
Nonfatal pulmonary embolism	1	4
Ante-mortem thrombotic disease without pulmonary embolism	3	2

Excluding these autopsied cases from the clinical analysis, the following clinical diagnoses remained:

TABLE 2. *Clinical Diagnoses in Deaths in Stocking and Control Groups.*

CLINICAL DIAGNOSES	STOCKING GROUP	CONTROL GROUP
Fatal pulmonary embolism	0	2
Nonfatal pulmonary embolism	1	8
Probable thrombotic disease without pulmonary embolism	13	9
Possible thrombotic disease without pulmonary embolism	20	18

Combining the clinical and autopsy data:

TABLE 3. *Combined Diagnoses in Deaths in Stocking and Control Groups.*

COMBINED DIAGNOSES	STOCKING GROUP	CONTROL GROUP
Fatal pulmonary embolism	0	4
Nonfatal pulmonary embolism	2	12
Definite or probable thrombotic disease without pulmonary embolism	16	11
Possible thrombotic disease without pulmonary embolism	20	18

Thus, it was apparent in both post-mortem and clinical analyses that pulmonary embolism was less frequent in the stocking group than in the control group but that thrombotic disease *without* pulmonary embolism was about equally common in the two groups.

"Out of Series" Cases

A note should be made concerning the "out of series" cases, because in this group (as already explained) were placed a number of patients with severe heart failure, a condition known to predispose to venous thrombosis and pulmonary embolism.[8, 9] Considering only the cases of thromboembolic disease proved at autopsy, there were 4 cases of *fatal* pulmonary embolism among the "out of series" patients, 3 of whom had massive peripheral edema due to congestive heart failure. In addition, six cases of *nonfatal* pulmonary embolism were proved at autopsy; of these cases 5 patients had congestive heart failure with massive peripheral edema. None of these "out of series" patients wore elastic stockings, although some of them did at first wear nonelastic stockinette and were later ruled "out of series" because at that time it was thought that such patients might develop pulmonary edema if they had by chance fallen into the stocking group and elastic stockings had been applied.

Thus, it was obvious that a high incidence of fatal and nonfatal embolism occurred in these "out of series" patients with marked peripheral edema due to congestive heart failure. Admittedly, this constitutes a serious objection to the value of the study, since it would have been most useful to know whether elastic stockings would have decreased the incidence of pulmonary embolism in this group. However, although no valid evidence was obtained on this point it was shown that the other methods in use in the hospital were not effective in preventing pulmonary embolism in this group, and since in milder cases of congestive heart failure elastic stockings did not cause difficulty it has been considered justifiable to include severe cases of congestive heart failure in the current trial. Therefore, at present every effort is being made to provide elastic stockings to such patients on admission to the hospital in the hope that this question will be answered.

Incidental Practical Information

In the course of this preliminary investigation much valuable experience was gained in the use of elastic stockings in hospital patients. For example, it was originally thought that the stockings should extend above the knee as far as possible and every effort was made to have them do so. In practice, however, it was found that the stockings would not stay smoothly placed above the knee but frequently rolled down and created a probably undesirable garter effect at the popliteal space. Accordingly, a knee-length stocking has been developed by Bauer and Black and is now used routinely in the current study. Likewise, stockings providing considerably higher pressures (up to 30 mm. of mercury) were originally considered preferable. However, as both clinical and laboratory experience was gained it became obvious that pressures above 10 to 15 mm. not only were unnecessary but were frequently intolerable for patients confined to bed.

Contraindications. The chief contraindication to the wearing of elastic stockings was the presence of ischemic vascular disease in the legs. In a previous study it had been shown that local compression above 10 mm. of mercury definitely and proportionately reduces the volume of blood flow in the limb.[10] In persons with normal circulation and at low compressing pressures these reductions of blood flow are inconsequential; however, in patients with incipient or actual tissue ischemia such reductions may be critical. For practical purposes it was found that the best rule was to refrain from applying elastic stockings to any patient with impalpable dorsalis-pedis pulsations. In all other cases repeated routine examinations were made to be sure that no signs or symptoms of ischemia were produced by elastic stockings. Also, emphasis was placed on applying only mildly compressive stockings, since tight stockings might produce more bad effects than good.

The next most common contraindication to the wearing of elastic stockings was the presence of ulceration, local inflammation or trauma of the legs. Obviously elastic stockings interfered with the proper routine treatment of these conditions and could not be used.

As regards massive edema of the legs, theoretically local compression would shift this edema centrally, possibly even into the lungs. For this reason great care was taken not to use elastic stockings in such cases; they were ruled "out of series." As already mentioned, the incidence of thromboembolic disease in "out of series" patients with edema due to congestive heart failure was high. On the basis of this original experience it was decided to try elastic stockings cautiously in such patients in the study now in progress; to date no obvious ill effects have been produced. In some such patients the edema has appeared to shift from the legs to the thighs, but no clear-cut instance of stocking-induced pulmonary edema has occurred.

Complaints. The most common complaints attributable to the wearing of elastic stockings were those presumably due to ischemia, namely, cold feet, aching or painful calves, sore skin and, rarely, hypoesthesia or anesthesia of the toes. Such complaints were much more common initially when tighter stockings were used and were invariably relieved by removing the stockings or replacing them with looser ones. In the study now in progress (using less compressive elastic stockings) such symptoms are exceptional. Indeed, many patients (particularly the elderly) comment on the comfort and support afforded by the stockings.

Discussion

From this preliminary trial a number of interesting points concerning thromboembolic disease in hospital patients have arisen. In the first place, the relatively uncommon occurrence of this complication in the general hospital population has again been demonstrated. In addition, its more frequent occurrence has been confirmed in certain conditions, particularly in the elderly, in patients with congestive heart failure and in those who have undergone major abdominal operations, especially for neoplastic disease. In line with the experience of Farmer and Smithwick[11] it was found possible to predict that 90 per cent of the pulmonary emboli would occur in a given 30 per cent of patients. Even with this degree of predictability, however, routine prophylaxis against pulmonary embolism by means of anticoagulants in this 30 per cent of patients is not practical. Furthermore, such prophylaxis would not be applied in the tragic cases of massive pulmonary embolism in relatively young persons otherwise nearly well, as after delivery, routine surgery or medical convalescence.

The present study was carried out to determine if elastic stockings, an economically feasible routine method, would reduce the incidence of thromboembolic disease. Statistical analysis showed the differences between the incidence of pulmonary embolism in the control and stocking groups, — calculated by the standard methods, which assume random sampling, — to be significant. Unfortunately, chiefly because of the relatively low incidence of the disease and the practical necessity of omitting certain severe cardiac cases from such an initial trial, this alternate-case study, although strongly suggesting a favorable effect from elastic stockings, is not regarded as definitely conclusive. Therefore, the study is now being continued, with every possible hospital admission (not alternate cases), even cardiac cases, included. This appears to have three advantages: More cases will be obtained; susceptible cardiac patients will be included; and the general demand from both patients and physi-

cians that all patients be covered will be satisfied. It is believed that the study reported here, as well as previous experience in this hospital,[11] will provide adequate background for control.

It is interesting that no instance of fatal embolism and only 2 of nonfatal pulmonary embolism occurred among the patients who wore elastic stockings. Obviously it could not be expected that even a complete suppression of thrombotic disease in the legs would abolish all pulmonary embolism, since in certain cases emboli are known to arise in the thigh, pelvis, abdomen, arms, neck or the heart itself. Indeed, 1 case of fatal pulmonary embolism has already occurred in the current study, in a patient who had undergone abdominal surgery for carcinomatosis. However, careful dissection of the veins in this case revealed no thrombi in the calves or thighs, although some were present in the prostatic plexus.

It is further interesting that the incidence of "probable and possible thrombosis without pulmonary embolism" apparently was not less and perhaps was even greater in the group who wore elastic stockings. However, this opinion must be taken with considerable reservation in connection with the clinical diagnoses, which, of course, were based largely on local symptoms. It seems likely that much of the aching or actual pain complained of was due to tight stockings, particularly early in this first study. In the study now in progress definite efforts have been made to loosen the stockings to provide a pressure of only about 10 to 15 mm. of mercury, and these complaints have virtually disappeared.

Conclusions

From this preliminary alternate-case study the following conclusions may be drawn:

The wearing of elastic stockings is practical as a routine procedure for hospital patients.

Elastic stockings do no harm if care is taken to apply them loosely (at 10 to 15 mm. Hg. pressure) and smoothly, and to omit them altogether in patients with ischemic vascular disease in the legs.

Elastic stockings apparently reduce the incidence of fatal and nonfatal pulmonary embolism in hospital patients.

No valid information was obtained in patients with massive peripheral edema due to congestive heart failure.

Further investigation of this method for the prophylaxis of pulmonary embolism seems warranted.

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STRESS INCONTINENCE TREATED BY VESICOURETHROPEXY*

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TRUE stress incontinence in women is most commonly seen after trauma to the vaginal walls incidental to childbirth. It is now generally accepted[1-3] that the cause of this incontinence and of that due to old age is the loss of the normal fascial and muscular supports of the vesical neck and urethra.

Kegel[4, 5] has described what he calls "physiologic therapy" for this distressing condition. His method is an office procedure that requires great patience and persistence on the part of patient and physician. I am sure that his many successes are the result of strengthened muscles, which raise the bladder neck to its proper position; in those cases in which I have tried it, however, I have been unable to duplicate his excellent results.

There are three possible surgical approaches to the problem: the many vaginal plastic operations, the suprapubic sling operations and the new suprapubic vesicourethral suspension or vesicourethropexy. Counseller,[6] reviewing a large series of cases of stress incontinence, concludes that vaginal plastic operations such as the Kelly and Kennedy procedures will give cures in approximately 85 per cent. There is no doubt that the vaginal approach should be utilized as the primary surgical procedure in all cases in which the vaginal walls need repair or in which there is associated disease of the uterus requiring vaginal hysterectomy.

The various suprapubic sling operations that have been devised by Aldridge,[7] Millin,[8] Shaw[9] and others have been aimed at providing correction for those cases of incontinence in which one

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or more vaginal operations have failed. However, these sling operations have all had certain disadvantages — chiefly their technical difficulty and the fact that the fascial slings frequently do not maintain sufficient blood supply and tone to serve the purpose for which they were devised.

Marshall, Marchetti and Krantz[10] in 1949 described a suprapubic operation of vesicourethral suspension to correct stress incontinence in cases in which previous surgery had failed; they use a preoperative test that has allowed them to select those candidates likely to be cured by the operation. Their procedure seems relatively simple and easy to perform and in no way disturbing to the blood supply of utilized structures. The Marshall technic consists essentially of introducing a No. 24 Foley catheter with 30-cc. balloon into the bladder and inflating the balloon. Through a suprapubic incision three sutures are placed equidistant from each other on either side of the urethra in the vaginal roof. Each of these sutures is then carried through the adjoining lateral wall of the urethra and through an appropriate area on the underside of the symphysis or periosteum of the pubis. Additional sutures are placed on either side of the vesical outlet and the anterior wall of the bladder and attached to either the pubic arch or the underside of the rectus muscles. The object is to elevate the bladder neck and to fix it and the urethra against the symphysis and the posterior surface of the rectus muscles. Marshall and his co-workers leave their catheters in place for seven days.

My first experience with this procedure occurred in October, 1950. The first patient on whom I used the Marshall technic had no complications and was completely cured. However, I was impressed by the risk that seemed inherent in passing a suture through the thin-walled urethra; therefore, when I treated a second case I sutured only the anterior vaginal wall (directly beside the urethra) to the underside of the symphysis. This seemed to me to fix the urethra in its correct position and to elevate the urethral meatus. Additional sutures were placed, according to the Marshall technic, in the lower segment of the bladder just above the vesical neck, fixing it to the undersurface of the rectus muscles. It also seemed to me that seven days' postoperative catheter drainage was unnecessary, particularly if it was reasonably certain that the urinary tract had not been entered by the suture material at any point. Therefore I left the catheter in place only three days in the second and subsequent cases. In one unusually difficult case I did not use the catheter at all in the postoperative period. Although there were no complications in this case, I think it is advisable, because of possible postoperative edema and increase in the residual urine, to leave a catheter in place for two or three days after the operation.

After these two modifications of the Marshall technic had been used with excellent results in three cases, Marchetti's article,[3] which he had published in 1949, came to my attention. He reported on 12 cases in which he had sutured the vaginal roof to the symphysis, avoiding the urethra, with completely satisfactory results. He removed the urethral catheter immediately after completing the operation and has noted no resultant complications. By means of cystograms Marchetti has clearly shown the elevation of the bladder and vesical neck that has been obtained by this operative procedure.

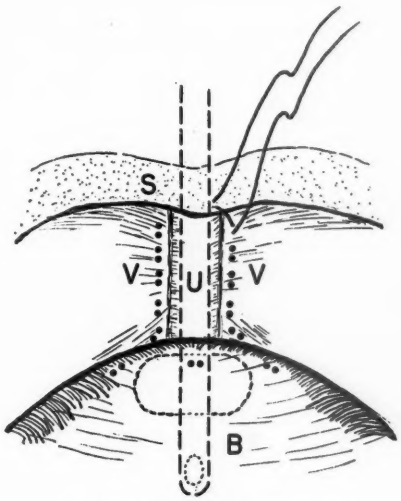

FIGURE 1. *Diagram of Suture Sites.*
S = *Underside of symphysis;* V = *anterior wall of vagina;* U = *urethra, with Foley catheter in place;* B = *bladder. The paired dots represent points of entrance and exit for each suture. The first (and deepest) suture on the right side is shown in place.*

My own series is limited to 6 cases. The patients' ages ranged from thirty-nine to seventy-two; all had incontinence of marked degree lasting from eight months to eighteen years. All except 1 had had at least one vaginal operation for relief of the incontinence, without permanent benefit. I believe that the test for incontinence described by Marshall is valuable; when tested by this method my patients showed positive results — that is, they leaked on coughing when standing with a full bladder and did not leak when two fingers introduced in the vagina on either side of the urethra supported the floor of the bladder and the vesical neck. Each of these cases herein reported has been followed for at least four months; in all except 1 patient the control of urine has been completely satisfactory since operation. The one exception, a fifty-four-year-old woman whose incontinence began

after a hysterectomy six years previously, was operated on February 5, 1951. She had perfect urinary control for the first two months after the operation, but her convalescence was complicated by bronchitis, and her postoperative period was made uncomfortable by persistent coughing. Two months after the operation she suddenly noticed the return of stress incontinence, and her condition now seems as poor as it was prior to the operation. Examination shows that she has developed a rather severe cystocele of the deep anterior vaginal wall; when she stands, the upper half of the vaginal wall bulges almost to the introitus, although the lower half, including the distal urethra, seems to maintain a normal position. It is my belief that this patient's sutures have given way; at present I plan a second operation, with vaginal repair of the cystocele, at an early date.

Summary

It has been shown that urinary incontinence due to childbirth injuries or to the hormonal changes of advancing age is accompanied by ptosis of the vaginal neck and failure of the normal supporting structures between the vesical neck, the urethra and the undersurface of the symphysis. Vaginal operations have proved of great value in correcting this condition in many patients but have been accompanied by failures in 15 to 30 per cent of the cases. Simple vesicourethral suspension, or vesicourethropexy, as described by Marshall, has proved a useful operation to correct most of these failures. Slight modifications in the operative approach have been described by Marchetti and have been tried independently in a small series of cases. These modifications seem to increase the safety of the operation and to shorten the patient's hospital stay. In 5 out of 6 cases operated on, the results have been completely satisfactory. The poor result in the sixth case is presumed to be due to failure of the sutures to hold, and another operation is contemplated.

Addendum

Since this paper was submitted for publication the unsatisfactory case has been reoperated with cure and a seventh case successfully completed.

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INDUSTRIAL DERMATITIS DUE TO CONTACT WITH BRASS

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CONTACT dermatitis from brass has not previously been reported. A survey of the literature fails to reveal any proved cases of this condition. Schwartz, Tulipan and Peck[1] failed to find any positive reactions to brass in patients they examined with so-called "brass poisoning." This evidence suggests that brass does not cause skin trouble. Other (Downing[2] and Klauder[3]) who have reported on large numbers of cases of contact dermatitis failed to report any due to brass.

With this array of negative evidence, it is not surprising then that the following cases were at first not recognized that the patients were not at first tested with brass or that the insurance companies were not willing to accept the entity of brass dermatitis without contest. With this in mind, 5 cases of proved brass dermatitis are reported from a total of over 2000 cases of industrial dermatitis observed. Five cases is not a large number, it is true, but nevertheless a hitherto unrecognized cause of dermatitis has been demonstrated. Industrial workers are even today refused treatment and compensation on the grounds that "brass has never been reported to cause a dermatitis." Now one must test with brass if it is suspected as a cause.

Brass is an alloy, containing approximately 2 parts of copper and 1 of zinc, with trace amounts of other elements (arsenic, tin, lead, antimony and nickel).[4] It is a common cause of "metal fume fever."

Of the important metal composing brass, copper has caused greenish discoloration of the hair, of the heavily keratinized portions of the palms and soles and of human perspiration[6] whereas the element zinc is not a reported cause of dermatitis in zinc foundries[7] although some zinc salts are irritants and sensitizers.[8]

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Case Reports

Case 1. M. N., a 42-year-old housewife, had worked for an electrical company for several months. Her job was to dismantle brass electrical fixtures and separate the parts. She stated that the rash had appeared on the right sole and on the outer side of the right foot and had subsequently spread to both feet and both hands.

On examination both palms and wrists were red and scaling and showed dried desquamating patches. Both soles were

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red and showed extensive vesiculation, with swelling and edema (Fig. 1). A diagnosis of "sensitization dermatitis probably due to sole leather" was recorded. Tests to sole and to shoe-upper leathers were negative. Tests to shoe-lining leather and to lining cement were also negative. These negative tests were considered to eliminate shoe leather as a cause of the dermatitis. Scrapings were negative for fungi, both on microscopical examination and by culture.

FIGURE 1. *Soles of Feet in Case 1 (Taken During Treatment).*

The patient was instructed to bring in the brass parts with which she worked for patch-test purposes. These brass parts were then cleaned with ether, washed with soap and water, rinsed and dried. They were left in place 48 hours.

FIGURE 2. *Patch-Test Site in Case 1.*

When they were removed the patch-test site was red and edematous and showed vesicles (Fig. 2). She was treated with cold compresses and soaks and removed from contact with brass. The condition slowly improved and cleared completely after about 3 months.

Chemical analysis of the brass showed its composition to be about 20 per cent zinc, 70 per cent copper, 1 per cent tin, 2 per cent iron, 1 per cent chrome and 3 per cent lead, with traces of manganese, nickel and silver.

The insurance company refused to honor the diagnosis and wished to wait 6 months after the condition had cleared to retest the patient. Accordingly, 6 months after she was discharged she was again seen and tested with brass screws, brass washers, pure copper and pure zinc. After 48 hours the brass-test site was red, edematous and vesicular. The copper-test site and zinc-test site were also positive.

The patient had from the first insisted that her rash was caused by the brass. She stated that the small washers had continually fallen into her shoes and had started the rash on her soles. However, since brass was not a known cause of dermatitis it was not deemed wise to test her with the brass until other factors had been ruled out.

CASE 2. L. B. had worked for a watch manufacturing company for 6 years as a machine operator. She ran an automatic balance machine. This machine cut out brass watch balances. Insoluble cutting oil was used as a coolant on this machine, and the patient's hands were continually oily. After machining, she dipped the balances into naphtha to clean them of oil. She denied any previous eruption, but she said that Trichlorethylene had "burned" her hands 3 or 4 years previously.

On examination the left 2nd, 3rd and 4th fingers and the right 5th finger were red, vesicular and eczematous. The feet were normal. A diagnosis of "contact dermatitis probably from naphtha" was made. She was tested with the insoluble oil but showed no reaction to this. The rash cleared and the patient was discharged before further patch tests could be made.

She was again seen some 5 months later; she stated that she had been laid off since her discharge from the physician's office, had not worked and had been free of any skin trouble. She later resumed her former employment, working with an automatic screw machine on brass parts; she again used an insoluble oil but had no contact with naphtha. After she had worked 5 days she noted itching, swelling, redness and blistering of the hands and fingers.

She was tested with the insoluble oil and with the powdered soap that she used at the shop. These tests were negative. She was then tested with a brass balance that had been cleaned with ether, trichlorethylene, soap and water. The test site showed redness and vesicles after 4 days. She was removed from contact with brass and the rash cleared. She returned for patch testing 3 months later and again showed a positive reaction to brass. She had a negative reaction to pure zinc but a positive reaction to pure copper. She has been free of any dermatitis for over 2 years but is not working on brass.

CASE 3. D. B., a 26-year-old woman, worked in a plating room setting up racks. Her hands were often wet with various solutions. She denied any previous eruption. She stated that her rash appeared first on the right forearm and subsequently on the hands.

On examination all the fingers were red, vesicular, moist, eczematous and slightly swollen. A diagnosis of "dermatitis venenata probably nickel sensitization" was made. A patch test to nickel was subsequently found to be positive. After the rash had cleared she twice returned to work with nickel plating; on both occasions a rash appeared, within 8 hours and within 24 hours, respectively.

She subsequently worked on aluminum in the same plant for 2 years without further eruptions. She was then assigned to handling brass, and a rash appeared within 3 weeks. She was patch tested with brass; redness and vesicles were seen at the site after 96 hours. She was retested 5 months later and again had positive tests for brass and copper but a negative test for zinc.

CASE 4. G. K. worked assembling brass toys for 3 weeks. On the 17th day she developed an erythematous vesicular eruption of the exposed parts of the forearms and arms. Tests for brass were positive.

CASE 5. D. A. worked in a brass foundry near two grinding wheels that continually showered a fine spray of brass filings over him. This caused him to itch, and after some months he developed a rash on the exposed parts of his neck, face and arms. After the eruption cleared he was tested with brass and had a positive reaction after 48 hours.

SUMMARY

Five cases of dermatitis from contact with brass are reported for the first time.

Brass, an alloy of copper and zinc, with traces of other elements, is well known as a cause of metal-fume fever, but dermatitis may also be caused by it.

The dermatologist should consider brass as a cause of some of the unusual dermatoses.

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MEDICAL PROGRESS

DISEASES OF THE THYROID GLAND (Part I)

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THE prompt application of recent chemical and physical knowledge of iodine to the study of the thyroid gland and the discovery and trial of the goitrogenic drugs have brought about prodigious progress in our understanding and treatment of disease of the thyroid gland in the past ten years. The background for this progress and its beginnings were recounted in the last progress report on disease of the thyroid gland, published in this journal in 1946.[1] The development in understanding of the chemical nature and elaboration of the thyroid hormone was reported. The discovery of the goitrogens and the initial therapeutic use of thiouracil were described. The preliminary ventures with radioactive iodine in the treatment of hyperthyroidism were recounted. The five years that have passed since that report was written have seen the fruition of these two new approaches to therapy. Surgery, time-honored master of the treatment of goiter, has now been challenged by the first truly successful nonsurgical therapies for hyperthyroidism. The attitude toward the treatment of thyroid cancer has also been revised. The question, therefore, that this progress report must try to answer is: What substance is there to these new therapies and how much of the treatment of goiter should pass from surgical to medical methods?

Answering this question will require the expression of an opinion. Enough time has not passed for us to be sure of our judgment in many matters of treatment. Knowledge of the thyroid gland is developing so quickly that what may have seemed settled yesterday is again open to question today.

Chemistry and Physiology of the Thyroid Hormone

The previous progress report on the thyroid gland reviewed in detail the chemistry and physiology of the formation of the thyroid hormone. Since then, — 1946, — there has been a broad elaboration of factual knowledge. None of the newly found facts, however, have departed sufficiently from those previously known for any radical shifts in concepts to have emerged. Newer chemical and physical methods have been used in the more recent investigations. For example, the radioactive isotopes of iodine have been widely utilized.[2, 3] They have been incorporated into the principle of chromatography in the study of the chemical steps involved in the formation and breakdown of the hormone.[4, 5] They have also been used in cytologic studies.[6-8] Those wishing a detailed review of these basic-science aspects, essential to understanding of thyroid disease, should first read the previous progress report[1] and then proceed to the following.

Harington, in his Richardson Lecture,[9] summarizes a chemist's lifelong investigation of the physiology and chemistry of the thyroid hormone. Means, in his Thayer Lectures,[10, 11] gives the clinician's perspective gained by thirty-five years of study of the thyroid hormone. He includes his latest concepts of iodine trapping, based on the current experiments of Wyngaarden, Stanbury and DuToit.[5]

A symposium on thyroid function as disclosed by newer methods of study has been held by the New York Academy of Sciences; the papers presented are published as an issue of their annals.[12] This is a remarkable issue, rich in experimental data. The phylogeny of the gland is described by Goldsmith.[13] De Robertis[14] and Dempsey[15] tell of their experiences in chemical cytology. Salter[16] summarizes his view of iodine metabolism. Chaikoff and Taurog,[17] Reineke[18] and LeBlond[19] write of other aspects of the thyroid hormone, and Albert[20] and Rawson[21] deal with the thyrotropic hormone. Astwood[22] and McGinty[23] review their observations on the antithyroid drugs. Many aspects of these reports will be referred to later.

A significant step has been added to our detailed understanding of the elaboration of the thyroid

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hormone. The capacity of the thyroid gland to concentrate the iodide ion, — the so-called iodine trapping, — has been differentiated from the gland's chemical ability to elaborate the iodine into the specific hormone. This differentiation has been accomplished by the selective use of goitrogenic drugs with different pharmacologic actions.

The thiocyanate ion, a known goitrogen,[24, 25] prevents the concentration of iodide within the gland.[26, 27] The thiouracil compounds, in contrast, allow the absorption of iodide but inhibit the chemical elaboration of iodine into the hormone (the so-called organic binding). It is believed that these thio- compounds block the formation of diiodotyrosine and the thyroxine molecule.[28] The use of radioactive iodine and the goitrogenic drugs in these studies is admirably reviewed by Raben and Astwood.[29]

New Methods of Studying Function

The availability of the radioactive isotopes of iodine, the means of measuring their radiations and the development of a precise chemical determination for inorganic iodine in the blood serum have extended the physician's opportunities for studying the function of the thyroid gland in its normal and diseased states. Prior to the advent of radioactive iodine and the precise chemical measurement, function was measured by the basal metabolic rate and by the so-called biologic methods, the measurement on microscopical section of cell characteristics such as mitotic figures, cell height and secretory globules. Now radioactive iodine has been introduced to measure the turnover of iodine in the thyroid gland — that is, the functional activity of the gland itself. The chemical measurement of iodine in its protein-bound fraction of the plasma indicates the amount of the hormone that the gland has already secreted. These two methods, with the basal metabolic rate, which measures oxygen consumption (and therefore the final rate of hormone action on the tissues), give three sequential views of the secretory activity of the thyroid gland.

Neither of the two new approaches has supplanted the determination of the basal metabolic rate as a diagnostic tool. They are no more accurate than the basal metabolic rate. They are made to deviate from the normal range by a different set of influences, however, and for this reason they are most informative diagnostic adjuncts. Unfortunately, they are more expensive and cumbersome procedures and therefore are less practicable than the basal metabolic rate.

The biologic methods of measuring function will undoubtedly continue to be used in experiments. They are currently essential to the study of thyrotropic activity.[14, 21, 30] Objective, quantitative measurement is too difficult and time-consuming for routine clinical use. The frequent clinical use of the goitrogenic drugs also makes them less reliable as measures of thyroid function. They have probably outlived their usefulness in clinical investigation[31-33] and therefore have already been replaced by the radioactive-iodine-tolerance test and the determination of the protein-bound iodine of the blood serum.

Radioactive Iodine

Experimentation with radioactive iodine has materially improved in the last five years, as a result of two technical developments. The first development was the increasing availability of radioactive isotopes of iodine with a longer half-life; the second was the improvement of instruments for measuring the radioactive emanations. The initial studies with radioactive iodine, which were reported in the previous review, were made with radioactive isotopes produced in the cyclotron.[34] These isotopes were more difficult to use than those now yielded by the piles. From the cyclotron bombardment of tellurium two isotopes emerged. The predominant isotope was I^{130}, with a short half-life of twelve and a half hours; only a small amount (10 per cent) of I^{131} had a longer half-life, of eight days. Therefore studies using this isotope mixture had to be made shortly after the bombardment. No storage of the isotope was possible. The laboratory had to be located close to cyclotron facilities. Experiments and therapy had to be prearranged with the physicist. When the isotope was used for therapy the entire dose had to be concentrated within a relatively few hours; frequently there was acute irradiation edema and soreness of the neck.[35]

With the development by the Atomic Energy Commission of radioactive piles at strategic sites throughout the country, these difficulties have been largely eliminated. Bombardment of iodine in the pile results in generous and predictable quantities of I^{131} that can be forwarded to distant places.[36] Storage is permissible for at least one or two half-lives. Another isotope of iodine with a half-life of approximately fifty-six days, I^{125}, has been isolated. Should this isotope be made available it would reduce further the management difficulties of experimentation if in other ways it were to prove as useful as I^{131}.

The construction of sensitive, reliable automatic counting instruments has also served to bring radioactive iodine to a clinical level.[37] The new instruments have ensured reproducible results accurate enough to be counted on as diagnostic tools and to safeguard therapy. The result of the availability of the longer-lived isotopes and sound instrumentation is that a large number of well equipped clinical laboratories in both this and other countries are now carrying out investigations of thyroid disease and the therapy of goiter.

The radioactive isotopes of iodine have been used in three ways to measure function. First, the isotope can be used as a tracer to measure the balance of iodine. This balance is a measure of the

turnover of iodine in the thyroid gland and is proportionate, under stable conditions, to the secretory activity of the gland. When a known amount of the isotope is given either by mouth or intravenously the test can be made in either of two ways or by the combination of both.[38-44] The amount absorbed and held by the thyroid gland added to that excreted in the urine in the first forty-eight hours has been found to be essentially identical with the amount administered. This so-called tracer study was first made in animals[2, 45] and later applied to man.[3, 46] Clinically, the balance taken up by the thyroid gland can be measured directly by placing suitable counting instruments over the thyroid gland or by measuring the reciprocal, that is, the amount excreted in the urine in the forty-eight hours following the administration of the iodine.

Secondly, the development of directional counting, — that is, counting by an instrument so shielded that it picks up the rays coming from only one direction, — permits the measurement of the activity of local areas within the thyroid gland. The activity of a single nodule, for example, can be compared with that of the non-nodular tissue.[47-50] Directional counting still has technical drawbacks and generally needs the attention of an expert physicist in order to be reliable.

TABLE 1. *Laboratory Findings in Certain Thyroid Disorders.**

DIAGNOSIS	BASAL METABOLIC RATE	SERUM PROTEIN-BOUND IODINE	RADIOACTIVE-IODINE UPTAKE
Normal or euthyroid	⟷	⟷	⟷
Thyrotoxicosis of Graves' disease	↑	↑	↑
Thyroid adenoma with hyperthyroidism	↑	↑	↑
Hyperthyroidism persisting on iodine	↑	↑	↓
Hyperthyroidism factitia	↑	↑	↓
Hyperophthalmopathic Graves' disease with euthyroidism	⟷	⟷	⟷
Primary myxedema	↓	↓	↓
Pituitary myxedema	↓	↓	↓
Iodine want	⟷	⟷	↑

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The third method of measuring function by radioactive isotopes is by radioautographs.[7, 8] Sensitive photographic film is laid in juxtaposition to thin slices of thyroid tissue removed from patients after they have been given a dose of radioactive iodine. Development of the film by the emanations is, of course, proportionate to the concentration of the radioactive iodine. The radioautographs can be compared with the microscopical sections, thus providing the pathologist an excellent tool for gauging function. The only drawback is that a relatively large dose of radioactive iodine is required to yield sufficient emanation for developing the film. Even the most sensitive films available need about 500 microcuries, a dose that probably has a measurable radiation effect on the thyroid tissue.[51] Such radiation is undesirable when the tissue to be excised is localized to one area, normal thyroid tissue being left *in situ*. This test has the obvious limitation that it can only be applied when an operation is indicated. It is also a test after the fact and therefore not a diagnostic one. The use of these three tests of function will be considered in greater detail below, under "Differential Diagnosis," "Hyperthyroidism" and "Tumors."

The radioactive isotopes of iodine are also used as a form of radiation therapy for goiter. They are ideal for this purpose when it is desired to inactivate hyperfunctioning cells. When it is desired to kill cells with little or no secreting activity, their value is questionable. These matters of therapy will also be discussed later, under "Hyperthyroidism" and "Thyroid Cancer."

Protein-Bound Iodine

A concerted attack by Salter, Riggs, Man, Curtis and their associates on the chemical determination of iodine in body fluids has resulted in a reproducible, clinically useful determination of the so-called protein-bound iodine or serum-precipitable iodine.[52-55] The determination is still technically very exacting, and its clinical use is limited by expense. Many thyroid clinics have now introduced it as a routine measurement despite the expense. It has become a necessity for those clinics carrying on active investigative programs.

Chaikoff has incorporated radioactive iodine with the serum precipitable-iodine determination.[56, 57] In animals he has used the amount of a tracer dose of radioactive iodine to be found after its passage through the thyroid gland in the protein-bound iodine of the blood serum as a measure of function. Clark, Williams, Friedell and their colleagues have applied this principle in the clinic to good effect, although it seems to have received little attention elsewhere.[58-60]

Use of the New Methods in Differential Diagnosis

The radioactive-iodine tracer, the chemical determination of the protein-bound iodine and the basal metabolic rate are a battery of tests offering unprecedented aid in the differential diagnosis of functional thyroid disease.

Means has reviewed their various permutations and combinations.[61] Tables 1 and 2 are reproduced from his paper; they show the widespread variety of possibilities found at the Thyroid Clinic of the Massachusetts General Hospital.

TABLE 2. *Laboratory Findings in Conditions Encountered in Differential Diagnosis of Hyperthyroidism and Hypothyroidism.**

DIAGNOSIS	BASAL METABOLIC RATE	SERUM PROTEIN-BOUND IODINE	RADIOACTIVE-IODINE UPTAKE
Anorexia nervosa	↓	↓	↓
Starvation	↓	↓	↓
Nonmyxedematous hypometabolism	↓	⟷	⟷
Hypermetabolism without thyrotoxicosis	↑	⟷	⟷
Dinitrophenol poisoning	↑	↓	⟷
Nephrosis	↓	↓	⟷
Pregnancy	↑	↑	?
Pheochromocytoma	↑	⟷	⟷
Leukemia	↑	⟷	⟷
Addison's disease	↓	⟷	⟷

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In true hyperthyroidism, — that is, excessive production of hormone by the thyroid gland of the patient, — all three tests register elevated function. In exogenous hyperthyroidism or hyperthyroidism factitia due to excessive intake of thyroid pills, a disease state sometimes associated with mental illness and troublesome in differential diagnosis, the tests no longer agree, and their manner of disagreeing provides proof of the diagnosis.[62] Since there is an excess of the hormone, the protein-bound iodine and the basal metabolic rate are elevated. The thyroid gland, in contrast, is at rest, and because of the lack of demand on the gland for hormonal output the tracer-iodine balance is normal or subnormal. Patients with this type of hyperthyroidism have had multiple operations on the thyroid gland in the mistaken belief that they had endogenous hyperthyroidism.

In an occasional case of pheochromocytoma the clinical picture of anatomic overactivity and nervousness resembles hyperthyroidism, and, to make confusion worse confounded, the metabolic rate is sometimes persistently elevated.[63, 64] This elevation of oxygen consumption is due to the constant secretion of adrenalin by the medullary tumor. In contrast to true hyperthyroidism, the radioactive-iodine tracer balance and the protein-bound iodine are normal.

The diagnosis of masked hyperthyroidism is often clinically difficult to establish in patients with cardiac insufficiency. In patients with primary cardiac insufficiency (not the cardiac insufficiency complicating thyrotoxicosis) the basal metabolic rate is often slightly elevated. This elevation is believed to be due to the pulmonary edema and extra work involved in respiration. The exclusion of hyperthyroidism as the primary or contributing cause of the cardiac insufficiency is more reliably carried out, therefore, by determination of the radioactive-iodine tracer balance and the protein-bound iodine. It should be pointed out, however, that an uptake by the thyroid gland of a normal proportion of a tracer dose of radioactive iodine does not necessarily exclude the presence of masked hyperthyroidism. Masked hyperthyroidism is a disease of older persons; its onset is insidious and its duration long. The goiter is usually nodular and well involuted (that is, well iodinated), and the avidity of such a goiter for iodine may lie within the normal range.[65]

Depression of the radioactive-iodine uptake by the thyroid gland obviously indicates reduced functional activity. Combined with the low value of the other two tests, it indicates true hypothyroidism or myxedema. Depression of the radioactive-iodine uptake in the thyroid gland also occurs when thyroid tissue is destroyed by thyroiditis or tumor. When this is found in thyroiditis it is generally transient, and at the same time the protein-bound iodine may be normal or even elevated, indicating an inflammatory extrusion of the preformed colloid into the circulation.[65-67] This condition in thyroiditis and the comparable one occurring in cancer will be considered later under each subject.

A refinement of the radioactive-iodine tracer study is the differentiation of primary and secondary hypothyroidism in conjunction with the thyroid-stimulating hormone of the anterior pituitary gland.[68] In primary hypothyroidism due to failure of the thyroid gland (so-called primary myxedema), the thyroid-stimulating hormone (TSH) fails to activate the thyroid gland and the turnover of radioactive iodine remains depressed. In hypothyroidism secondary to anterior-pituitary failure the thyroid gland responds to the stimulus of TSH and the avidity, or turnover, of radioactive iodine is increased. The differentiation of these two types of hypothyroidism is important and clinically is often difficult. Inadvertent use of a full replacement dose of thyroid in the patient with anterior-pituitary hypothyroidism may plunge the patient into Addisonian insufficiency. With the probability that TSH will soon be available in a purified state comparable to that of ACTH, this differential test may be expected to assume clinical importance.

Proper use of the radioactive-iodine tracer balance as a diagnostic test of function depends on knowledge of the iodine environment in which the patient has been living. The thyroid gland of a normal person living in a nongoitrous area such as the Eastern seaboard absorbs from 35 to 50 per cent of the administered tracer. The average daily intake of iodine of such a person is 100 microgm. The thyrotoxic goiter of a patient who has been given the same amount of iodine will absorb 55 to 95 per cent of the tracer dose, the amount depending on the severity of the thyrotoxicosis. If the patient has been receiving a greater intake of iodine as intended therapy or inadvertently (in cough medicine, for example), the avidity of the goiter for the tracer is reduced. This circumstance was mentioned earlier in regard to the involuted goiter of masked hyperthyroidism.

The contrary circumstance is found in persons living in iodine-deficient areas who are not receiving supplemental iodine. In a classic study of the iodine metabolism of persons living on a low intake of iodine, Stanbury, Riggs, Brownell and their Argentinian associates have shown that the avidity of the thyroid for the radioactive-iodine tracer may in some persons lie in the toxic range.[69] Studies were made on clinically normal inhabitants of the goitrous area of the Argentine, some of whom were living on but 10 microgm. of iodine per day. Their thyroid glands seized with extraordinary rapidity from 85 to 99 per cent of the tracer dose — an avidity comparable to severe thyrotoxicosis in New England.

The comparative estimation of function in different portions of the same goiter by means of the

directional counter also offers an opportunity for diagnostic refinement. A nodular area with depressed function may indicate localized thyroiditis or a malignant lesion. (These will be referred to later.) A nodule with intense function close to soft thyroid tissue with depressed function indicates a hyperfunctioning nodule with atrophy of the uninvolved tissue.[8, 32, 70] This finding may at first sight seem academic, but since the therapeutic management of a hyperfunctioning adenoma is different from that of the diffusely hyperplastic goiter of Graves' disease the preoperative identification of such a nodule serves to orient the surgeon to the problem he faces at operation. The problem of the treatment presented by the hyperfunctioning adenoma will be discussed later under "Advantages of the Surgical Treatment of Hyperthyroidism."

(*To be continued*)

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MEDICAL INTELLIGENCE

NEEDLE BIOPSY IN BONE LESIONS

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NEEDLE biopsy is a well known and in some places a well established procedure, but it is probable that it is not widely enough used and that its advantages, particularly in the diagnosis of bone lesions, are not generally appreciated.

Needle biopsy is of two distinct types; it is important to understand their differences. At the Memorial Hospital in New York City various workers[1] have perfected and reported on a method that they have found successful. An 18-gauge needle is introduced into the mass and by a combination of suction and motion tiny bits of tissue are drawn into the lumen of the needle. The material so obtained is smeared on a slide and the histologic diagnosis is made from this stained specimen. The method requires a competent pathologist who has had considerable experience in examining such smears. It is probably safe to say that pathologists in the smaller centers do not have the opportunity to develop this facility and are therefore justified in their rejection of the method for their own use.

The other type of needle biopsy is quite a different matter. It is this method that is described and advocated in this paper. By means of a large-bore trocar-like needle with a serrated tip a plug of tissue is removed that is large enough to be sectioned and stained by the usual methods and therefore presents no unusual problem of microscopical diagnosis. The Turkel[2] needle, the needle devised by Wrenn and Feder[3] and that designed by Valls, Ottolenghi and Schajowicz[4] are all effective; all three are used at the Elliot Hospital.

Needle biopsy of bone lesions is consistently successful; the same cannot be said of tumors located in soft tissue. This is because in soft tissue one cannot be sure of the location of the point of the needle. In bone lesions, on the other hand, the location of the point can be ascertained either by touch or by x-ray.

This method enables one to establish a positive diagnosis in certain cases in which clinical, x-ray and laboratory findings would otherwise be the sole diagnostic aids, as in lesions of the vertebral bodies or in elderly or debilitated patients with osteolytic or sclerosing lesions of bone. It substitutes a minor, easily tolerated procedure for what is often a major operation, as, for example, in any deep-seated bone lesion. For the same reason more patients will agree to biopsy if they know that it merely involves the introduct on of a needle under local anesthesia rather than a knife under general anesthesia. The tremendous financial saving to the patient may also be mentioned in this connection. Operation expenses are less, and in many cases costly x-ray and laboratory study can be eliminated by this simple, direct approach to a microscopical diagnosis. Needle biopsy is safer. The small but ever-present mortality of operation under general anesthesia is avoided. The severe hemorrhage that may occur when some tumors are incised is easily controlled when a needle is introduced. And, as a final point, post-biopsy growth of tumor tissue is probably less likely to develop along a needle track than through an operative wound.

The technic of obtaining a plug of tissue has two requirements. First, the operator must be certain that the needle tip is actually in the diseased tissue. If necessary, this can be verified by x-ray. If the mass can be palpated or if there is a cavity for the needle to enter, x-ray control is usually not required. Secondly, the operator must be satisfied that he has actually obtained plugs of the desired tissue and not merely blood clot or shreds of fat. If the contents of the needle are extruded into a small basin of sterile normal saline solution, the pieces of tissue sink to the bottom and are easily identified.

The patient is given a sedative and narcotic. The usual sterile precautions are taken. The skin

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is anesthetized with 2 per cent novocaine and punctured with a knife. Ordinarily no structure beneath the skin needs to be anesthetized. If the lesion is within 2 inches of the skin, the Turkel needle is used. The large outer needle is pushed firmly into the bone, the stylet withdrawn and the serrated needle introduced. This latter needle is advanced and rotated at the same time. A syringe is attached and suction applied. Suction with rotation cuts the specimen from the surrounding tissue. The suction is released and the needle withdrawn from the cannula. The specimen is ejected from the needle with the stylet. This proceeds smoothly when the specimen is firm or contains bone substance. If the tissue is friable, suction may be applied with rotation as the needle is advanced and may be continued as the needle is withdrawn.

For the deep-seated lesions the longer needle is used. It has a pointed stylet; this point is pressed firmly into the bone. The position of the needle is checked by x-ray. If a cavity is to be entered, the normal overlying bone can be penetrated by the pointed stylet and then removed. The syringe is attached and suction applied. The needle is advanced and rotated at the same time. On withdrawal the suction should be released before the needle tip is free of the skin; otherwise, the specimen will be splashed over the inside of the barrel of the syringe. The syringe should not be flushed into the basin of saline solution, as it then becomes discolored by blood, which makes it difficult to find the pieces of tissue. The specimens should always be placed in the basin of solution, never on a piece of gauze. From the solution they are transferred immediately to the fixative.

The whole process should be unhurried and painstaking, with the operator's attention concentrated on the location and movement of the point of the needle. In some areas, of course, care must be taken lest the needle injure an important structure.

In some lesions tissue may be difficult to obtain, and one may instead aspirate fluid, blood, purulent exudate or gelatinous material, any of which may suggest the diagnosis. The value of inserting a needle into a mass is so great that it should be considered as a routine procedure.

Case Reports

Case 1. S. W., a 60-year-old man, had pain in a foot for 1 year. X-ray examination showed a destructive lesion of the talus that had broken through the cortex. Needle biopsy yielded abundant tissue typical of benign giant-cell tumor.

Case 2. A. L., a 45-year-old woman, had had a radical mastectomy for carcinoma 2½ years previously and complained of severe pain in the right hip. X-ray examination revealed a destructive change in the right ilium. Needle biopsy yielded tissue that showed typical adenocarcinoma.

Case 3. M. L., a 55-year-old woman, had had pain in one hip for 6 months. X-ray examination revealed destruction of the ilium; a large soft-tissue mass was seen laterally. Needle biopsy caused severe bleeding, which was brought under control by pressure. If open operation had been performed for the biopsy it is likely that the hemorrhage would have been uncontrollable. Within a day or so the needle biopsy was repeated; this time the tumor was entered tangentially. Tissue was obtained that showed a few distorted glandular structures formed by pale vacuolated epithelial cells, suggestive of a renal carcinoma. X-ray films of the kidney showed a mass in the lower pole on the left.

Case 4. C. T., a 70-year-old man, had had a transurethral prostatic resection. There was no evidence of cancer in the tissue examined. Fifteen months after operation he developed pain in the pubic region. Rectal examination revealed a hard, nodular prostate gland. X-ray examination showed a sclerosing process in the pubic bone. The possibilities were Paget's disease, metastatic carcinoma and osteitis pubis. A bone plug was easily obtained with the needle; this showed adenocarcima, probably from the prostate gland.

Case 5. L. M., a 65-year-old man, had had asthmatic symptoms for some time. X-ray films disclosed a lesion in the lung. He also had lower-back pain; x-ray examination revealed a destructive lesion in the posterior elements of the 1st, 2nd and 3rd lumbar vertebras. Under x-ray control the needle point was placed at the proper site; tissue was removed that showed metastatic carcinoma, probably primary in the lung.

Case 6. H. P., a 68-year-old woman, had had a radical mastectomy for carcinoma 14 years previously. She complained of backache of 6 months' duration. X-ray examination showed a destructive lesion in the posterior elements of the 3rd lumbar vertebra. The needle was introduced under x-ray control, and tissue was obtained that revealed metastatic carcinoma.

These two cases of metastatic carcinoma of the spine had involvement of the posterior elements of the vertebras, which region is easily accessible to the needle devised by Wrenn and Feder. When the lesion is in a vertebral body the biopsy needle is introduced according to the technic described by Valls, Ottolenghi and Schajowicz. A special set of needles is required. This method was employed in Case 10.

Case 7. R. G., an 8-month-old infant, had a swelling of the elbow with the clinical characteristics of tuberculosis. Syphilis, tumor and osteomyelitis were also considered. General anesthesia was necessary in this case. The position of the needle was checked by x-ray. Material was removed that proved to be granulation tissue infiltrated with polymorphonuclear leukocytes. Culture of the tissue yielded a staphylococcus. (Culture and biopsy should be taken at the same procedure in all cases.) Antibiotic therapy was instituted. Incision and drainage were not performed, as no purulent material was aspirated. Two months later the elbow was essentially normal.

Case 8. C. W., a 30-year-old woman, had pain in the left hip. X-ray examination revealed a cystic lesion in the head of the femur. Giant-cell tumor and solitary bone cyst were considered. The needle was introduced under x-ray control. The entry of the point into the cavity could be felt. Abundant tissue was removed; it proved to be cartilage and fibrous connective tissue. This was probably a cyst of degenerative origin; such cysts commonly develop about the hip joint.

Case 9. J. D., a middle-aged man, was in a highly debilitated state. X-ray examination showed a pulmonary lesion in the right apex and a destructive area in the clavicle. Needle biopsy yielded tissue that showed squamous-cell carcinoma. (The pathologist who made the microscopical diagnosis was skeptical of the method and had had no previous experience with tissue obtained by a needle. He confessed that examination of the tissue presented no problem.)

Case 10. L. B., a 59-year-old man, had had a destructive lesion involving the bodies of the 12th dorsal and 1st lumbar vertebras for 1 year. Tuberculosis, cancer and osteomyelitis were considered. The biopsy needle was introduced into

the lesion according to the technic of Valls, Ottolenghi and Schajowicz. The specimen obtained showed nonspecific granulomatous inflammation but no tubercles. Purulent material was also aspirated through the biopsy needle from the paravertebral abscess. Smears and cultures of this showed tubercle bacilli.

Summary

Deep-seated lesions in bones and joints are easily and successfully biopsied by the use of special needles. The tissue obtained is sufficient in quantity to be examined by the usual microscopical technics.

Appreciation is expressed to Dr. George C. Wilkins for introducing us to the procedure of needle biopsy and showing helpful interest in our efforts.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38101

Presentation of Case

A forty-nine-year-old woman entered the hospital because of loose bowel movements.

The patient had a twenty-year history of mild epigastric pain, with some nausea and vomiting, and intolerance to fried food. One year prior to admission, because of increasing severity of the symptoms, a cholecystectomy was done, with relief of the symptoms for a short time. Seven months prior to admission the patient noted a change in character of the epigastric pain, which became sharper. The pain occurred in episodes, once or twice a day, lasted ten to fifteen minutes and on some occasions radiated to below the right scapula. These attacks had no relation to meals and occurred during both night and day, sometimes awaking her. Four months prior to admission she noted a burning epigastric pain that occurred fifteen to twenty minutes after meals. With this she was frequently nauseated and at times vomited bile-stained material, with relief of the pain. At about this time she first noted loose stools; these at first occurred only one or two days a week but later in periods of three to four days of diarrhea alternating with two to three days of obstipation or at most one formed stool. The loose stools were accompanied by abdominal cramps and at times by tenesmus; during the periods of obstipation the abdomen increased in size and then decreased with the onset of the diarrhea. The stools were thick, grayish-yellow, liquid, foamy and foul smelling; bloody mucus or greasiness had not been noted. As the severity of the symptoms gradually increased, three months prior to admission the patient was placed on a bland diet and given medicine. She continued to have diarrhea, epigastric pain and abdominal cramps; six weeks before admission she entered another hospital, where she remained for five weeks. Deep pigmentation of the skin of the hands, chin and legs was noted. The hemoglobin was 71 per cent and the red-cell count 3,660,000. There were 13 eosinophils in the smear of blood taken when the patient was in a fasting state. The serum sodium was 138.7 milliequiv. and the potassium 4.7 milliequiv. per liter; 2.88 mg. of 17-ketosteroids were excreted in 24 hours. A Kepler water test was normal. The patient received two blood transfusions, folovite, reticulogen, liver injections, iron tablets, paregoric and a bland low-fat diet, but there was little change in her condition. She had lost 25 pounds in weight and was becoming progressively weaker. The diarrhea and abdominal pain remained unchanged.

Eleven years before admission she had a supravaginal hysterectomy for "fibroids." Two years prior to admission she had an attack of rheumatoid arthritis that lasted five months and subsided during gold therapy. In the winter of that same year and in the following winter she had had attacks of "pleurisy." There was no previous history of diarrhea.

Physical examination revealed a thin woman with a diffuse yellowish-brown pigmentation of the skin; the deepest pigmentation was in palmar creases and operative scars. The heart and lungs were normal. The abdomen was protuberant and the epigastrium was somewhat tender. No masses or organs were felt.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 50 diastolic.

The urine was normal. Examination of the blood showed a red-cell count of 3,260,000, a white-cell count of 10,900, with 94 per cent neutrophils, and a hemoglobin of 9.0 gm. A hematocrit was 24 and the mean corpuscular volume was 73 cu. microns. The serum sodium was 130 milliequiv., the chloride

97 milliequiv. and the potassium 3.0 milliequiv. per liter; the total protein was 4.7 gm., with a normal albumin-globulin ratio, the blood calcium 7.8 mg., the amylase 23 units, the alkaline phosphatase 9.6 units and the nonprotein nitrogen 20 mg. per 100 cc. A bromsulfalein test and a prothrombin time were normal. The eosinophil count was 9 cells per cu. mm. in the fasting state, 48 cells per cu. mm. four hours after ACTH (adrenocorticotrophic hormone) injection. The first few stool specimens were guaiac negative, but subsequent specimens were consistently guaiac + to ++++. No undigested meat fibers were seen on microscopical examination of the stools. There was an increase in neutral and combined fats in the stools. Two- and three-day stool collections showed a total daily fat content varying from 15.77 to 23.05 gm. and a total daily nitrogen content varying from 1.88 to 2.68 gm. A gastric analysis showed no free hydrochloric acid. No tumor cells were seen in a cytologic examination of the duodenal drainage. The duodenal contents were collected for 45 minutes after the injection of 50 cc. of 20 per cent

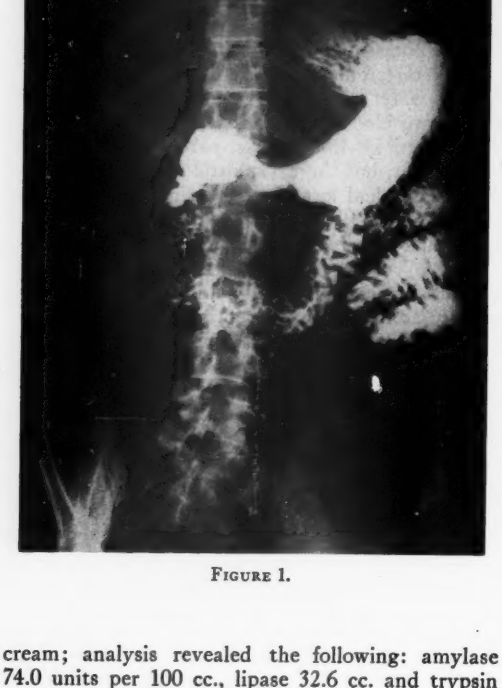

FIGURE 1.

cream; analysis revealed the following: amylase 74.0 units per 100 cc., lipase 32.6 cc. and trypsin 35 per cent. A gastrointestinal series showed a dilated duodenum (Fig. 1) and abnormal segmentation of the jejunum, with pooling of the barium (Fig. 2). The mucosa of the duodenum and jejunum appeared to be coarse and wide.

During the period of investigation the diarrhea continued unabated, the stools being greasy and foul. On the tenth day intravenous injection of ACTH was begun; three days later her appetite had returned and she was gaining weight and strength rapidly. During the next week she continued to improve; there was mild pedal edema and

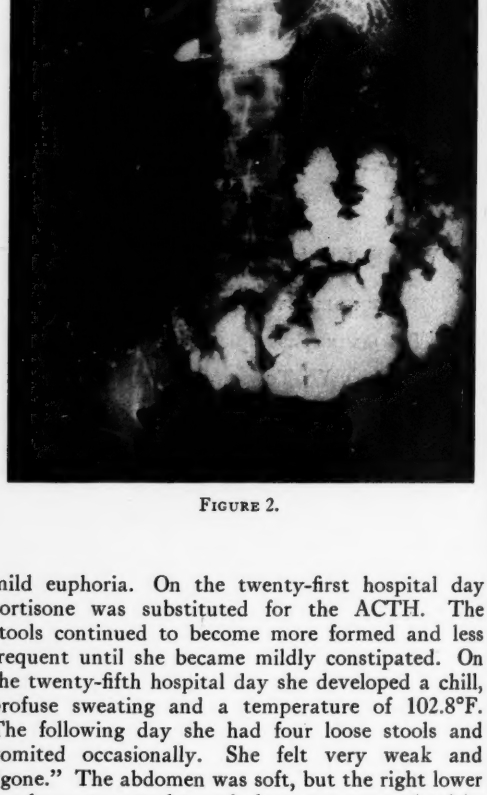

FIGURE 2.

mild euphoria. On the twenty-first hospital day cortisone was substituted for the ACTH. The stools continued to become more formed and less frequent until she became mildly constipated. On the twenty-fifth hospital day she developed a chill, profuse sweating and a temperature of 102.8°F. The following day she had four loose stools and vomited occasionally. She felt very weak and "gone." The abdomen was soft, but the right lower quadrant was tender and there was no peristalsis. The blood pressure was 90 systolic, 70 diastolic. The following day an occasional abortive peristaltic tinkle could be heard, and 24 hours later the abdominal tenderness was less and subdued peristalsis could be heard. The vomiting and diarrhea persisted. On the twenty-ninth day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FRANZ INGELFINGER*: Before reading this history I wish to point out that this is a case presenting severe diarrhea with fat loss, — that is, stea-

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torrhea, — as a result of which the patient went rapidly downhill. I think it helps, in hearing a history, to be oriented as to the major difficulty so that significant details may be appreciated. Dr. Chester Jones, Dr. Culver and their associates have been interested in a gastric factor as related to the steatorrhea that may follow gastrectomy, but this is usually not a cause of major steatorrhea. Severe steatorrhea is caused either by hepatobiliary insufficiency, by pancreatic disease or insufficiency or by diffuse intestinal disease that impairs the absorbing surface. As I read through the history, let me see if I can select points that indicate one or the other of these three major causes of steatorrhea.

Dr. Chester M. Jones: May I make one comment? The pigmentation of the skin was so dark, — it was yellowish-brown, — that she had been taken for a Negress by some persons who had not seen her previously.

Dr. Ingelfinger: I am happy to hear that, as yellowish pigmentation is relatively rare except as a result of jaundice or exposure to certain chemicals, but brown in various shades of intensity is quite common in a number of intestinal disorders. Now, with respect to the three possible causes of major steatorrhea, I shall dismiss disease of the hepatobiliary system, because the patient had no jaundice and the albumin-globulin ratio, prothrombin time and bromsulfalein test showed no evidence of liver disease.

Let me go on to pancreatic insufficiency. I do not believe this patient primarily had a pancreatic insufficiency for the following reasons: In the first place, she had rather variable pain. Suppose she had a carcinoma of the pancreas; then the carcinoma would obviously have had to be of the body or tail, since she had no jaundice. When pain develops in this disease, it is a prominent feature and does not migrate over the abdomen and change its character as it did in this case. As there appeared to be relatively little back radiation of this patient's pain, it did not seem to be the pain that I usually associate with carcinoma of the body or tail of the pancreas. Such pain may vary from patient to patient, but in any one patient it will tend to be fairly constant. In chronic pancreatitis the pain might be like this, but this patient went downhill too rapidly for that disease. Deep pigmentation is a rare feature of pancreatic insufficiency, even when patients have considerable steatorrhea because of it.

An analysis of the stools showed that there were no undigested meat fibers and that the twenty-four-hour fecal loss of nitrogen was less than 3 gm. Thaysen[1] has given us 3 gm. as a magic figure, a daily loss of nitrogen below 3 gm. being said to indicate steatorrhea not caused by pancreatic disease, whereas a loss of more than 3 gm. is said to occur in pancreatogenous steatorrhea, for in this condition tryptic as well as lypolytic function is impaired. Although I think it risky to put too much trust in such sharply differentiated levels, nevertheless the facts that the patient had no meat fibers and put out less than 3 gm. of nitrogen in the stools are both good arguments against pancreatic disease.

As far as the analysis of the duodenal contents is concerned, I asked a spy to inquire discreetly what was considered normal here at the Massachusetts General Hospital. He started at a technician level and ended at the physician level, but no one could tell him. If you asked me what is normal at the Massachusetts Memorial Hospitals, I would say: "I will call so-and-so and let you know in a day." So many different methods are used, so many different stimulants are used, — cream, in this case, — and so many variable periods of collection are used, that it is difficult to know what is normal. No matter what is normal, however, there appears to be some pancreatic activity, as evidenced by these tests, and the finding of some pancreatic activity, even if less than optimum, does not favor the possibility that this patient's steatorrhea was pancreatogenous. Furthermore, although I know that the Massachusetts General Hospital staff is interested in investigation, the fact that ACTH rather than pancreatic extract was used to treat this patient is an indication that they did not consider the duodenal enzyme studies indicative of pancreatic insufficiency.

Why do I discount the results of the enzyme determinations on the duodenal contents as a sign of pancreatic disease, even if the values reported should be considered low? Because by the time pancreatic disease has caused as much steatorrhea and weight loss as this patient had, any pancreatic-function test would show practically no enzymatic activity whatever. Severe steatorrhea of pancreatic origin requires severe impairment of pancreatic function, and consequently a moderate or even low normal pancreatic enzyme output would not be consistent with severe pancreatogenous steatorrhea. These considerations induce me to eliminate the pancreas as responsible for this patient's difficulties.

Let us go on to insufficiency of the intestine itself. An obvious cause of steatorrhea is a short circuit of the small intestine. But I have no reason to suspect that this patient had some entero-enterostomy that permitted food to by-pass a large area of gut. I have to suppose that she had some disease of the intestine interfering with the absorption of food — particularly of fat. A great many findings suggest an Addisonian type of picture: pigmentation, weakness, loss of weight. We know that patients with Addison's disease may have bizarre gastrointestinal manifestations; nevertheless, there are certain arguments against either an adrenal or a pituitary disorder. The blood pressure

was never very low. One year before admission the patient easily survived cholecystectomy. The serum sodium and potassium were not at levels found in Addison's disease. The 17-ketosteroid excretion was low, indeed, but it is low in many advanced debilitated conditions. The fecal loss of fat is also in excess of that usually found in Addison's disease. Although many physicians have tried to relate the adrenal cortex to fat absorption, the relation appears tenuous. In the untreated Addisonian patient a low eosinophilic count is usually not found. Finally, the proof that the patient responded well to ACTH and cortisone is good evidence that she did not have either adrenocortical or pituitary insufficiency. Pigmentation is a common feature, moreover, of chronic small-intestine insufficiency. Many patients with sprue, some with ulcerative colitis and some with ileitis have extensive pigmentation. The fact that the patient had pigmentation to such a degree that she was mistaken for a Negress, — which I must admit I have never seen, — is not incompatible with an intestinal disorder.

What was the intestinal disorder? The most common small-intestine disorder is regional enteritis or jejunoileitis, a more diffuse variant of the same disease. Did she have that? Usually this disease does not cause such extensive steatorrhea. Steatorrhea of intestinal origin usually indicates a very diffuse disorder, and even if half the intestine were peppered with granulomatous jejunoileitis, steatorrhea would not be so prominent. The most striking argument against regional enteritis is, however, the essentially negative x-ray report. Possibly this would be a good time to ask to see the films.

Dr. Stanley M. Wyman: The important films, those of the upper gastrointestinal tract, show a duodenal loop that is a little larger than usual, but I am not able to define compression of the loop in local areas (Fig. 1). There is definite increase in the thickness of the individual folds throughout the duodenal loop as well as in the jejunum and well down into the ileum. The film taken at 30 minutes clearly shows so-called segmentation of the barium column in the lower jejunum and ileum. This is even better seen on a later film, as Dr. Ingelfinger has predicted (Fig. 2). I can recognize no areas of localized narrowing or dilatation of small bowel. I think the bones are quite osteoporotic for a woman of this age; that is perhaps part of the general nutritional picture.

Dr. Ingelfinger: There are no features characteristic of regional ileitis. If she did not have regional ileitis, did she have sprue? You would say this picture is consistent with sprue, I take it?

Dr. Wyman: Yes.

Dr. Ingelfinger: Sprue is a disease the nature of which is unknown. There are many characteristic features of sprue in this case — particularly the steatorrhea, the absence of marked fecal nitrogen loss, the downhill course and the suggestive traces of Addison's disease. The + to ++++ guaiac test on the stools is an argument against sprue. In the absence of bleeding tendencies from prothrombin deficiency, I would not expect a positive guaiac test. However, the strongest point against sprue is this patient's failure to respond to all the vitamin B factors she received. If the patient had developed sprue *de novo* about a half a year before she entered this hospital and was then treated intensively with the various B factors that are listed, she should have shown some improvement. In sprue patients who have had the disease for years such treatment is relatively disappointing, but in a new case a more rapid improvement and some response to vitamin B-complex therapy would be expected.

A number of diffuse granulomatous conditions of the small intestine could give this picture: tuberculosis, sarcoid, Hodgkin's disease, nonspecific granulomas and a condition called Whipple's disease. To save time I shall confine my discussion to Whipple's disease.[2] This case is a classic example of Whipple's disease, — if any condition of which there are only 15 to 30 cases reported in the literature can be said to present classic features, — with one exception that I shall discuss last. The patient's history is really too good. Whipple's disease is a granulomatous condition of the small intestine leading to steatorrhea and the accumulation of fat particles in the granulomatous reaction. Whipple's disease is characterized almost invariably by an antecedent arthritis; this patient had arthritis. Frequently there are pleural or pericardial reactions or chronic cough; this patient had pleurisy on two occasions. Many believe that Whipple's disease is a diffuse polyserositis or collagen type of disease in which the intestinal manifestations happen to be the major but not the only manifestations. The weight loss and pigmentation, the suggestions of Addison's disease without actual Addison's disease, the variable abdominal pains shifting around — all these you can find in Whipple's disease. The normal albumin-globulin ratio with low albumin and low globulin is characteristic. A number of these patients have had cholecystectomies — as in this case, without benefit. The stool examinations and the + to ++++ guaiac tests are typical of Whipple's disease. So are the marked hypochromic anemia and the x-ray picture. To repeat, this patient is a classic case of Whipple's disease except for one thing — and here I raise the ugly head, although not in the usual sense, of sex. Alas and alack for me, this has been almost purely a male disease so far — and this patient was a female.

What about the patient's response to ACTH and cortisone? My guess is that the patient responded to the treatment but perforation in the lower small bowel took place and peritonitis ensued to account for the symptoms described. Why did

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she not have more reaction to the peritonitis? Patients given ACTH or cortisone apparently have an indolent type of intestinal perforation; her reaction is what you might expect if perforation occurred during ACTH or cortisone therapy.

I would be inclined to say, in spite of the reported incidence, that this woman had either Whipple's disease or something fairly similar to it — a diffuse granulomatosis with the accumulation of fat and macrophages along the intestine, possibly pericardial and pleural adhesions and a peritonitis produced by an intestinal perforation.

DR. WALTER BAUER: Would you want to include any type of connective-tissue disease in the diagnoses?

DR. INGELFINGER: Scleroderma, lupus erythematosus and polyarteritis nodosa may all present bizarre intestinal manifestations. As far as I know, steatorrhea is not so marked. In this patient the reason I did not consider scleroderma was that she apparently had neither skin changes nor esophageal symptoms. Although I am ready to make a diagnosis of intestinal scleroderma in the absence of skin changes, I think she ought to have had an esophageal component before scleroderma need be considered seriously.

DR. WYMAN: I think that is a very important point.

DR. BAUER: I know Whipple's disease from the literature; I have never seen a case, but I think Dr. Ingelfinger will agree with my belief that it is a very hard diagnosis to prove at the clinical level.

DR. INGELFINGER: Absolutely. At a clinical level one can only make a diagnosis of diffuse granulomatous disease of the intestine as opposed to pancreatic disease and sprue.

DR. BAUER: You will further agree that many of the cases of so-called Whipple's disease could just as well fall into the connective-tissue-disease group. In those cases in the literature without pathological proof one is rather hesitant to accept the diagnosis. Would you agree to that?

DR. INGELFINGER: Yes; of course, many physicians believe that Whipple's disease is a variant of connective-tissue disease.[3] Furthermore, many have defined Whipple's disease according to their own criteria. There is one excellent article,[4,5] however, that established such strict criteria that Whipple's original description is said to be excluded.

DR. JONES: I think Dr. Ingelfinger's discussion has been orderly and superb. We tried to follow the same reasoning, but I am sure the engine knocked somewhat harder than Dr. Ingelfinger's did as he discussed the case here. The patient was sent into the hospital after a careful work-up with a tentative diagnosis of sprue. The pigmentation was extraordinary, and outside the hospital the attempt had been made to rule out adrenal insufficiency. We were confident that it was not adrenal insufficiency, and the response to ACTH pretty thoroughly ruled that out. I believed she did not have sprue for about the same reasons that Dr. Ingelfinger gave. The acute attack of severe abdominal pain and fever and chills worried us because we thought that a perforation had occurred and was partly obscured by the use of corticosteroids. Dr. Richard Warren saw the patient with me and we decided against operation. About ten days to two weeks later, while the patient was still on corticosteroid therapy, we decided to operate; she had had so much pain that we wished to be certain that no local disease was causing partial obstruction that could be treated. After watching the patient for 48 hours we were sure that she did not have peritonitis. The preoperative diagnosis was Whipple's disease. I might add that the stool-fat figure does not give the entire story. Actually, the original stool fat was about 40 to 50 per cent of ingested fat. After the use of corticosteroids, this had dropped down to a fairly normal figure — about 5 per cent.

CLINICAL DIAGNOSIS

Whipple's disease.

DR. INGELFINGER'S DIAGNOSES

Whipple's disease.
Perforation of intestine with peritonitis.

ANATOMICAL DIAGNOSIS

Whipple's disease.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: I am sorry that Dr. Richard Warren cannot be here, but he sent a colored slide of the operative findings. Dr. Jones, you were at the operation; perhaps you would describe the small bowel.

DR. JONES: The picture was extraordinary. From the ligament of Treitz to about the midileum the bowel was greatly thickened, but the thickening diminished toward the cecum; it was almost the equivalent of a cellulitis. All the lacteals were full, and they could be clearly seen as creamy-white pathways. All the highlights here represent fat in the lacteals, and in some places it almost looked as if the lacteals had burst; there was a diffuse spread of fatty material underneath the serosa. In the root of the mesentery covering the drainage from the ligament of Treitz down to the midileum, the lymph nodes were between two and three times normal in size; they were white. One was excised; when it was squeezed creamy material actually came out of it. There was also what we had suspected but had not proved — a chylous ascites; there was about a liter to a liter and a half of chylous fluid in the cavity. At operation a segment of bowel, including its mesentery and lymph nodes, was removed en bloc.

In this low-power view of an ordinary hematoxylin-and-eosin stain of the mucosa of the ileum, you notice that the epithelium is intact; scattered through the entire tunica propria are large monocytes with small nuclei and a lot of pink-staining foamy cytoplasm (Fig. 3). The section of the lymph node shows, in addition to the markedly distended lymphatics, these same large clear cells. Since the lymphatics appeared to be filled with fat, the fat stain was the first special stain we did, expecting to find these large monocytes stuffed with fat droplets. The fat stain did show some fat droplets but not in these big cells; most of it is between the cells, and there are many areas in the mucosa where there is no fat. In other words, most of the fat was interstitial. The distended lymphatics in the lymph nodes were filled with fat, and some monocytes contained fat droplets; this lipid droplet stained pink with Nile blue sulfate, revealing the presence of glycerides. A periodic-acid Schiff stain for polysaccharides shows that these foamy cells in the bowel epithelium and most of those in the lymph nodes are Schiff positive and do not contain fat (Fig. 4). This is not a new finding. It was described a year or so ago by Black–Schaffer,[6] who emphasized the fact that this material was not sudanophilic. He believed the material was a glycoprotein. Dr. Agustin Roque, of our laboratory, repeated the Schiff reaction after saliva digestion, and it did not change; hence this material is not glycogen.

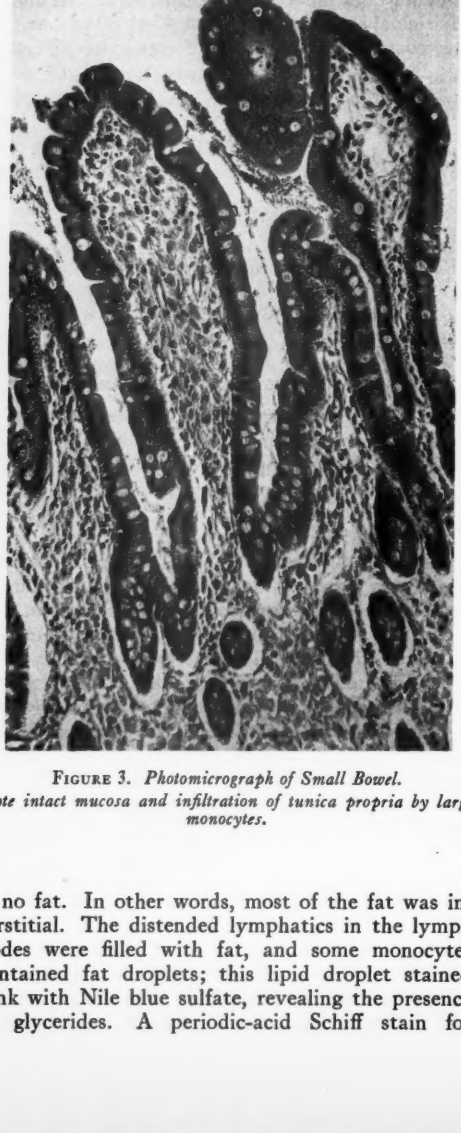

FIGURE 3. *Photomicrograph of Small Bowel. Note intact mucosa and infiltration of tunica propria by large monocytes.*

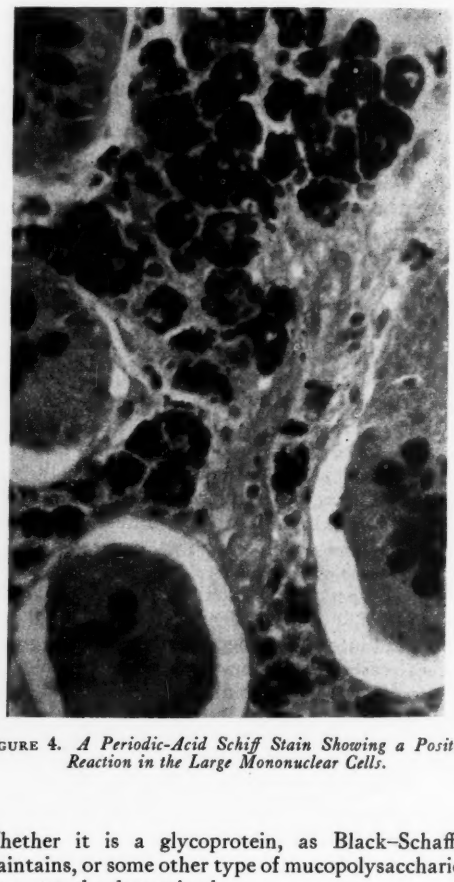

FIGURE 4. *A Periodic-Acid Schiff Stain Showing a Positive Reaction in the Large Mononuclear Cells.*

Whether it is a glycoprotein, as Black–Schaffer maintains, or some other type of mucopolysaccharide has yet to be determined.

This brings up the question of the real etiology of this disease. Most of the investigation has been based on the idea that the fatty material in the intestines and the lymph nodes is due to an obstructive phenomenon and is related to the cause of the disease. Perhaps that is only a secondary phenomenon and the primary condition is dependent on a defect in the intestinal epithelium itself, leading to an inability to absorb fats. If we could find out exactly what is in these cells we might get a clue to the cause of the disease. It has been sug-

gested by Black-Schaffer that the disease should be called not lipodystrophia intestinalis, — a name offered by Whipple originally, — but merely Whipple's disease. It is interesting to note that in the original paper Whipple described these "foamy" cells as being "in the neighborhood of fat deposits." Although he emphasized the large fat vacuoles in the mucosa, submucosa and lymph nodes, he carefully stated that these "foamy" cells were free from fat. This observation seems to have been ignored.

DR. INGELFINGER: In going through the literature, one gathers that chylous ascites has been found particularly in females. Females who are not accepted by some physicians as cases of Whipple's disease actually had what this patient had — dilated lacteals and some chylous ascites. It is interesting that this is another female patient with prominent lacteals and chylous ascites.

DR. JONES: I should like to make one comment. Since operation the patient has done extremely well. The steatorrhea has nearly disappeared; on an intake of about 110 gm. of fat by mouth she loses only 5 gm. in the stools, which is essentially a normal figure. Corticosteroids were stopped after the operation and were withheld for a month. She had no further diarrhea, pain or distention, and the fat content of the stools remained at a low level. Since that time she has again been given corticosteroids for purposes of study. My belief is exactly like yours — that the idea that Whipple's disease is due to a blockage of the lacteals, with consequent inability to absorb fat and excessive loss of fat in the intestinal contents, is probably an incorrect or incomplete concept. I think it is much more likely that in this disease there is a disturbance of mucosal-cell activity in the intestine, — or possibly at a submucosal level, — with a striking change in intestinal function. Probably what we have done in this case is similar to what we have done in intractable sprue — that is, we have changed the mucosal-cell activity to the extent of restoring toward or to normal the function of these cells, which among other things have to do with the absorbing of fat. I think it is much more important than the mere absorption of fat as such. I think it means an alteration of cell dynamics and function. Because the cell dynamics were abnormal there was an abnormal handling of fat, and it was caught in the lacteals in excessive amounts. It is altogether too early to predict what will happen to this patient, but I think it is the first time that a dramatic change in symptoms, signs and laboratory findings has been produced by any form of therapy. The depth of pigmentation has diminished so that she is much less dark now than eight weeks ago.

DR. CASTLEMAN: It is possible that these mononuclear cells contain a lipoprotein, which would be Schiff positive but would not take any of the fat stains — a condition analogous to that of the Gaucher cell. The latter contains kerasin, a galactolipoprotein, which is also Schiff positive.[7]

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CASE 38102

PRESENTATION OF CASE

A sixty-two-year-old man was admitted to the hospital because of severe chest pain.

Four years before admission the patient had had an episode of intense substernal pain that radiated to the left shoulder and upper arm and persisted for about a week. He was kept in bed for a period of three months, during which time the pain recurred frequently and was relieved by nitroglycerin. Following this he continued to have similar episodes of substernal pain brought on by exertion, excitement or the eating of heavy meals; usually the pain was relieved promptly by nitroglycerin, but on several occasions this gave no relief. In the course of the four years he spent several one-to-two-week periods in bed. Three days before admission, while eating, he suddenly developed precordial pain, similar to that which he had had in the past but more severe. The pain was made worse by deep breathing and was not relieved by nitroglycerin. He was given an injection by his physician, but the pain was only mildly relieved.

On physical examination the neck veins were slightly distended. The chest was normal. There was precordial tenderness. The heart did not appear to be enlarged. There was a split first mitral sound but no murmurs or arrhythmia. The abdomen was negative and there was no peripheral edema or calf tenderness.

The temperature was 101.4°F., the pulse 104 and the respirations 22. The blood pressure was 110 systolic, 9 diastolic.

The urine had a specific gravity of 1.020 and gave a ++ reaction for albumin; the sediment contained a rare hyaline cast. The white-cell count was 20,200, with 70 per cent neutrophils, and the hemoglobin was 15.3 gm. The nonprotein nitrogen was 29 mg. and the cholesterol 274 mg. per 100 cc. The prothrombin time was 16 seconds (normal, 14 seconds). The electrocardiogram showed a normal rhythm at a rate of 80, a PR interval of 0.16 second, a QRS interval of 0.12 second and normal voltage.

The R waves were wide and slurred in Leads AVL, V_5 and V_6; the S waves were wide and slurred in Leads 3, AVF, AVR, V_1, V_2, V_3 and V_4.

He received morphine and oxygen, without much relief. On the day following admission a transitory grating friction rub was heard in the lower anterior left chest just to the left of the nipple; splinting of the left chest and tenderness in the left calf were found. He was given 50 mg. of heparin subcutaneously and 200 mg. of dicumarol orally daily for two days. The day following the last dose, the prothrombin time was 22 seconds (normal, 14 seconds) and the patient was feeling better except for slight precordial pain. Suddenly he became cold, sweaty, ashen and aphasic. On examination the head was turned to the right, the eyes were deviated to the right and right-facial weakness, right ptosis and flailing of the left arm and leg were observed. There were no changes in the reflexes. The blood pressure was 120 systolic, 90 diastolic and the respirations were Cheyne–Stokes in character. The following day he responded to questions and seemed somewhat improved. He subsequently showed a well marked left hemiplegia and dysarthria. His condition was unchanged, although he seemed to be gaining strength, until the thirteenth day, when he suddenly called out, became unresponsive and pulseless within a few minutes and died. An electrocardiogram made two days before death had shown no significant change.

Differential Diagnosis

Dr. James H. Currens*: This elderly man had a history of having had an episode of chest pain four years previously that was of considerable severity, persisting for about a week. It is quite unusual for pain to persist for a week; therefore I prefer to believe it was intermittent rather than sustained pain. In any event, it was of sufficient gravity to suggest to either his physician or the patient himself that he should stay in bed, which he did for three months. In view of present-day methods of treatment that seems like an unusually long period of bed rest. It seems apparent that he probably had a myocardial infarction and that he subsequently had what is best described as angina decubitus resulting from coronary heart disease. That is all in the past.

Apparently this patient did quite well until he developed severe chest pain three days before he came into the hospital. I should like to call your attention to the fact that the pain was described as being precordial pain, which means different things to different physicians and is, I think, usually a poorly chosen term used to describe the pain of angina. That the pain was aggravated by deep breathing is a little disturbing if one wishes to attribute it to a recurrence of myocardial infarction. However, since the pain was said to be similar to the pain he had previously I should prefer to believe that it was sufficiently similar to be due to a recurrence of myocardial infarction. There was a lapse of three days between the last information that I am given about the patient and his entry to the hospital. I should like to know how long the pain lasted; what sort of treatment he had; and why he was not admitted to the hospital immediately if he was thought to have suffered a myocardial infarction. However, these things are perhaps not pertinent, and all I know is that again, as was his custom in the past, he undoubtedly went to bed and remained in bed for three days.

Physical examination suggested some distention of neck veins, which would be in keeping with failure of the heart, but I do not know the position of the patient at the time the examination was made, so it might not be of significance. Precordial tenderness in a person who has had heart disease for a long period of time is often a difficult sign to evaluate, and I doubt if it was of much help in this particular patient. On entry there was fever, rapid pulse and leukocytosis — all suggesting infarction of either the lung or the heart. The rest of the laboratory examinations are not of much help. The electrocardiogram indicating impairment of the interventricular conduction is of no help in attempting to differentiate myocardial infarction and those changes seen in association with acute cor pulmonale or acute pulmonary embolism; it merely indicated a rather diffuse involvement of the heart from one of several possible causes.

During the course in the hospital, there were three significant events. The first was the finding on the second hospital day, — the fifth day after the pain,— of a friction rub in the left lower anterior chest, with some splinting of the left chest, suggesting that breathing was painful. Certainly the most likely explanation for such a pleurisy is pulmonary infarction secondary to a small pulmonary embolism. One might ask whether, in the presence of myocardial infarction, a friction rub might not

*Assistant in medicine, Massachusetts General Hospital.

be expected. The fact that the friction rub was heard so far laterally over the chest would suggest involvement of the pleura rather than the pericardium. Evidence that might substantiate the possibility of a pulmonary infarction was the tenderness in the left calf. Tenderness is frequently absent with thrombosis in the leg veins, but when present I think it is an important finding.

The second important incident during the course was the rather sudden development of sweating, ashen color and aphasia. It seems to me that the two possibilities to explain the sudden onset of what later developed into a cerebrovascular accident with left hemiparesis are embolism and hemorrhage. One might argue, because the prothrombin activity was somewhat reduced, being about 35 per cent, that he might have had a cerebral hemorrhage on the right to account for the subsequent development of the left hemiplegia. Bleeding at that prothrombin level is unlikely, and I think that in the absence of more definitive evidence for subacute bacterial endocarditis it can be discarded; to my knowledge, hemorrhage into the brain does not occur during the administration of dicumarol unless there is associated bacterial endocarditis. A subarachnoid hemorrhage may occur — but not hemorrhage in the localized fashion, of which there was evidence here. I should therefore prefer to consider this a cerebral embolus; the source of the embolus may have been mural thrombi secondary to the myocardial infarction of the left ventricle.

The third significant event was, of course, his death; it is stated that he called out, became unresponsive and pulseless and died rather suddenly. I think that there are three possibilities to explain the sudden death. Rupture of the myocardium must always be considered in a person who has had a myocardial infarction, but the rupture of the myocardium sixteen days after the onset of myocardial infarction would be somewhat unusual, as most myocardial ruptures occur within ten days to two weeks. After two weeks a good deal of fibrous tissue has been laid down, and the myocardial wall is considerably stronger. The most common explanation of the sudden death might be cardiac arrhythmia or cardiac arrest, and I do not think we have any good knowledge of which of these is the more common. There was fairly good evidence in the history that the patient had had a previous pulmonary embolism resulting in pulmonary infarction, which would perhaps make another diagnosis more likely. I prefer, then, to believe that this patient had a rather large pulmonary embolism that was the cause of his sudden death.

A dissecting aneurysm should, I believe, always be mentioned when a person has had chest pain and died suddenly. The absence of previous hypertension would certainly argue against that. The patient did have cerebral symptoms. Although it is very unusual, I think that if any of you heard Dr. Berg's excellent presentation here about a year ago* you will recall that cerebral symptoms are possible in the presence of dissecting aneurysm of the aorta.

The treatment with anticoagulants was inadequate; if Dr. Castleman describes what I think was present, — that the patient had repeated emboli or thrombi in both venous and arterial systems — then I think it unfortunate that he did not receive more vigorous anticoagulation treatment. The statistical evidence is quite convincing that one can save lives by giving dicumarol to patients over the age of sixty who have had myocardial infarction. My diagnosis would be coronary-artery disease with two myocardial infarctions, one recent and one old; cerebral embolus from a mural thrombus; and venous thrombosis with a small early pulmonary embolism and a large fatal pulmonary embolism.

DR. EARLE M. CHAPMAN: Did you consider a sudden hemorrhage into the pericardium?

DR. CURRENS: Rupture of the myocardium was one of the possibilities that I did mention.

DR. BENJAMIN CASTLEMAN: You meant rupture of the myocardium rather than the pericardial hemorrhage that you might see associated with the use of an anticoagulant.

DR. CHAPMAN: That is what Dr. Kranes and I were discussing. It would be hard to blame the dicumarol for it because of the time interval; as I understand it from the record, the patient received the treatment for two days and did not die until eleven days after the last dose. Is that correct?

DR. JAMES J. FERGUSON: The anticoagulants were started the day after admission. It was the following day, or about twenty-four hours later, that he had the development of the hemiplegia, and thereafter the anticoagulants were stopped.

DR. CASTLEMAN: Because of the hemiplegia?

DR. FERGUSON: Yes.

DR. JACOB LERMAN: Did you consider another embolus to the brain?

*Case Records of the Massachusetts General Hospital (Case 37112). *New Eng. J. Med.* 244:412-414, 1951.

DR. CURRENS: With a cerebral embolus one does not die as rapidly as this man did. It is certainly a possibility.

CLINICAL DIAGNOSES

Myocardial infarction.
Cerebral embolus.
Pulmonary infarction.

DR. CURRENS' DIAGNOSES

Coronary artery disease.
Myocardial infarctions, old and recent, with mural thrombus.
Cerebral embolus.
Pulmonary embolus, old, and recent fatal.

ANATOMICAL DIAGNOSES

Myocardial infarction (16 days) with mural thrombi.
Rupture of myocardium with cardiac tamponade.
Cerebral embolus.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The apex of the heart and a large part of the interventricular septum were infarcted, and there was a yellowish-gray mural thrombus quite adherent to the endocardium. The apex bulged a little and contained 2 linear tears through which blackish blood clot protruded; this had produced a hemopericardium, which was the cause of death. The microscopical appearance of the infarct shows that there was a lot of healing; it appeared consistent with an infarct of sixteen days and one that would not be expected to rupture. There were, however, throughout the infarct so many large islands of necrotic muscle fibers that still were unabsorbed that I am quite sure they contributed to the softening of the myocardium and allowed a rupture. It is fortunate that the patient did not receive adequate anticoagulant therapy, as I am sure the death would have been blamed on it. The cerebral lesion was a large infarct of the right parietal lobe, undoubtedly caused by an embolus from this mural thrombus. There were no infarctions or emboli in the lungs and no pleurisy. What was heard was undoubtedly the friction rub of the pericardium.

DR. CURRENS: Would you say the myocardial infarction was larger than the usual variety of myocardial infarction?

DR. CASTLEMAN: Yes; it was much larger. The infarction was really beginning to form an aneurysm in this early stage. It was healing well enough, except for the presence of so much necrotic muscle in between the areas of healing. We did not find any evidence of an old infarct in other parts of the myocardium.

DR. REED HARWOOD: At what stage does a rupture of the heart usually occur?

DR. CASTLEMAN: At about seven to ten days. I have seen them at two days, and they have been reported at five weeks.

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GENERAL PRACTICE CLINIC

DR. PAUL WILLIAMSON, the director of the General Practice Clinic recently established at the University of Tennessee, has briefly sketched and analyzed some of the criticisms that have been directed at that highly publicized worker in the vineyard, the general practitioner. The purpose of the Clinic is to conduct an intensive program of training in general practice, with the added duty of bringing to the attention of the profession both the advantages and disadvantages, the weakness and the strength of this particular type of service.

The general practitioner, since extremes are rarely realistic, certainly deserves the degree of criticism that he has received no more than he probably desires the heady adulation that has also been his lot in recent years. He is, and will undoubtedly continue to be, the family adviser in times of sickness and of stress and the arbiter of family problems. With the general return to an appreciation of his indispensability in a society that recognizes the individuality of its members, his position remains secure — at least under the present system of delivering medical care, which is probably less susceptible to attack than even its protagonists believe.

No activity, however, whether of general practice, specialization, human relations or even medical journalism, should be allowed to settle into a status quo. Like an old mattress, it needs occasionally to be picked over, vacuum-cleaned and rebuilt, with the addition of some fresh horsehair, or feathers.

Dr. Williamson, in a recent communication, not only lists the common criticisms of the general practitioner but gives the reasons for them — and some of the answers. Obviously, none of the criticisms apply to all, but in general they concern matters in which the practitioner is considered vulnerable.

These criticisms refer to the volume of work that the general practitioner, especially in the country districts, is called upon to do — a burden so great that he can supposedly carry none of it well; to his failure to keep up with medical progress; to his failure to refer cases early enough in their course to be benefited by the specialist; and to his tendency to undertake types of practice for which he is not trained.

To whatever degree they may be justified, these criticisms touch on two basic obstacles that every such practitioner must avoid if he is to achieve the fullest development and attain the most effective distribution of his resources. These handicaps are overwork, which can be remedied only by a better deployment of available medical personnel, and overconfidence, which results from the independence of his position in the community. He must do so many things unaided or else leave them undone that he develops a self-reliance that tends to hypertrophy. Like the lord of a small domain, he may on occasion come to harbor the idea that he can do no wrong.

The cure for this condition, before the hypertrophy becomes permanent, is for him to get out and see

the world of medicine, both in the pages of the journals that he has given up reading and through the postgraduate refresher courses that are becoming so widely available. In the consciousness of his indispensability he must be aware also of his fallibility.

UNDIAGNOSED OR SUBCLINICAL BRILL'S DISEASE?

Although the earliest reports of the recognition, clinical description and some of the major epidemiologic features of Brill's disease emanated from New York,[1, 2] the most significant observations concerning its etiology and possible epidemiologic implications have been made at Harvard by Zinsser[3, 4] and, subsequently, by a number of his pupils. Indeed, the first isolation of typhus rickettsia from a case of Brill's disease was reported by Zinsser and Castaneda[3] in this journal in 1933, some twenty years after the earliest clinical report by Dr. Roger I. Lee[5] of the cases of this disease observed at the Massachusetts General Hospital.

More recently Murray and Snyder,[6] of the Harvard School of Public Health, characterized, according to the most precise methods now available, 7 strains of typhus rickettsia that they isolated between 1947 and 1949 from typical cases of Brill's disease. They and a group of collaborators in Boston, New York and Philadelphia also described the clinical and laboratory features of these cases in considerable detail.[7] The 7 strains of typhus rickettsia were isolated in each instance by allowing human body lice to feed on the patient during the early, acute and febrile stage of the illness. It is of special interest that 3 of these strains could not be isolated from blood obtained at the same time and inoculated into susceptible cotton rats and guinea pigs.

From the observations made in these 7 patients and in 7 additional patients who were first seen at later stages of the disease and in whom the diagnosis was made on clinical and serologic grounds but who failed to yield the rickettsias by all available methods, Murray and his collaborators drew the following conclusions: A clinical diagnosis of Brill's disease should be considered in any foreign-born patient who has lived at some previous time in an area where typhus appears in epidemic form, when that patient has a fever of unknown origin, complains of intense, persistent headache and displays a macular or maculopapular rash on the fourth to the sixth day of the disease. The laboratory confirmation of this clinical diagnosis should be made by the complement-fixation test (or the rickettsial-agglutination test). The Weil–Felix reaction, according to their observations, can be completely ignored if it is negative. They believed that the use of these diagnostic criteria by physicians should result in recognition of more cases of Brill's disease, particularly among the displaced persons coming to the United States from Europe. They also believed that patients with Brill's disease can infect human body lice with typhus rickettsias, and their observations strongly suggested that patients with Brill's disease could initiate epidemics of typhus if they lived in a louse-infested community.

It is to be recalled that in 1934 Zinsser,[3] on the basis of his collected epidemiologic and laboratory data, developed the hypothesis that Brill's disease represents a recrudescence of an old typhus infection originally acquired in Europe. This hypothesis implied that rickettsias, once acquired, remain latent for many years somewhere in the tissues of the infected human being. It follows that cases of Brill's disease occurring in louse-infested communities could become the foci of small or large outbreaks of epidemic typhus. Thus man, through the medium of patients with Brill's disease, might be the reservoir of epidemic-typhus rickettsias, serving to maintain the disease between epidemics over the centuries. Some of the arguments and objections advanced by a number of workers against Zinsser's hypothesis were reviewed by Murray and his co-workers.[7] Most of these objections have been answered by the recent studies of the Harvard workers.

In this issue of the *Journal* there appears another paper from the workers at the Harvard School of Public Health, in collaboration with physicians at the Beth Israel Hospital. The findings reported therein add another link to the chain of evidence supporting Zinsser's hypothesis. The data pre-

sented in this paper suggest the possibility that Brill's disease might also occur in an unrecognized form or that the diagnosis of the clinical form may be missed in some cases.

By careful and detailed serologic studies, Murray and his co-workers were able to show that some 34 to 40 per cent of a group of 50 foreign-born patients at the Beth Israel Hospital who were immigrants to the United States from typhus zones of eastern Europe had had previous contact with typhus rickettsias. They suggest that probably more of these patients had such contacts and that this might be demonstrated if more sensitive technics could be devised. They have not been able to demonstrate epidemic-typhus antibodies, even by the most sensitive tests now available, in any persons born in North America, except those who had received typhus vaccine.

Some serums reported on in the present study had specific antibodies for epidemic typhus in rather high titers. This led the authors to speculate that the high titers in some patients might have been the result of a recent attack of Brill's disease — that is, that these patients had had a recrudescence of the original typhus illness within two years prior to the time that the serums were obtained. This speculation is based on the fact that complement-fixing antibodies usually fall below the titer of 1:80 within two years of a primary attack of louse-borne typhus; the sera from 11 of their patients had titers of 1:80 or higher, although the patients had been in this country for twenty-seven to sixty years. They also quote other observations made recently in Yugoslavia that indicate that an infection with another rickettsia, namely that of Q fever, does not produce an anamnestic rise in epidemic-typhus antibodies when it occurs in persons who have residual antibodies to epidemic typhus. It therefore seems unlikely that the high titers demonstrated by Murray and his associates were the result of such an anamnestic response to any other type of infection.

The authors point out the fallacy of depending on a history concerning an illness such as typhus fever if the infection occurred many years previously. They also call attention to the fact that such high residual titers as they observed, — 1:80 to 1:160, — obtained in a random population of foreign-born persons who might be considered candidates for Brill's disease, indicate great caution in diagnosing an acute attack of Brill's disease from a single serum specimen. They emphasize the importance of obtaining a rising titer in successive blood specimens or titers as high as 1:1000 or more before attributing diagnostic validity to the specific serologic test.

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6. Murray, E. S., and Snyder, J. C. Brill's disease. II. Etiology. *Am. J. Hyg.* **53**:22-32, 1951.
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SALUTE TO *DIABETES*

In these days, when a specialty journal seems to be springing like a leprechaun from under every lithotype, one might ordinarily be concerned over the appearance of still another. With a million diabetics under treatment in the land, however, with another million undiscovered and with the sugar bowls of the nation filled to overflowing, one can only applaud the decision of the American Diabetic Association to proceed with the publication of its own new journal, the first issue of which appeared in January.

This new publication, — it need scarcely be called a venture, — is edited by Dr. Frank N. Allan of Boston, with a group of assistants and a board of editors under the chairmanship of Dr. Charles H. Best of Toronto — all strategically located so far as geography is concerned.

The editors have wisely devoted a page to the purposes of the journal and advice on manuscript specifications. One would scarcely consider this to be necessary, but the persistent disregard of basic rules of manuscript preparation by occasional

authors leads to the suspicion that not all of them have read papers already published or have access to journals that might serve as guides for their literary efforts.

Dr. Elliott P. Joslin, honorary president of the American Diabetes Association, opens the number with a "Salute to *Diabetes*." He brings this introduction to a close with the timely, — and timeless, — injunction of Archbishop Isidore of Seville:

Disce ut semper victurus, vive ut cras moriturus.

Learn as if you would live forever, live as if you would die tomorrow.

The new journal continues with seven practical original articles, an ample number of abstracts of the literature on diabetes, three editorials, a biographical note on Arnoldo Cantani, the great Italian pioneer in the modern treatment of diabetes, and a section of book reviews. The Organization Section contains an exposition of the objectives of the American Diabetes Association by its president, Dr. Arthur R. Colwell, of Chicago; the address delivered last June by the retiring president, Dr. Lester J. Palmer, of Seattle; a statement of the role of the diabetic in civilian defense; association news; and obituaries.

It is a pleasure for the *New England Journal of Medicine* to welcome this newcomer to the nursery, and, — perhaps with the hope of some kind of reciprocal action, — with kind words to cheer it on its destined course.

VOLUNTARY EVALUATION OF LABORATORIES

A SYMPOSIUM on the problem of providing adequate numbers of well trained medical technologists for hospital laboratories was published in the February 8, 1951, issue of the *Journal*. The Massachusetts Department of Public Health column in the present issue features a report that indicates some of the accomplishments resulting from the efforts of such laboratories to improve their skill in diagnostic bacteriology and serology. This achievement is largely due to the voluntary co-operation of technologists and pathologists in the examination of test materials sent periodically to each laboratory enrolled in the program. A number of the technologists have now enrolled in refresher courses in various laboratory diagnostic subjects.

Workers in diagnostic laboratories should welcome reasonable control of the accuracy of their work. The approval program of the Department of Public Health provides a unique opportunity to check the media, reagents and technical skill of laboratories in various bacteriologic and serologic procedures. Workers in laboratories participating in the program are to be commended for their conscientious efforts — especially in view of their heavy work load, regrettably so common in medical laboratories at the present time.

Spiritual Rapping Mania. — *If reports are to be relied upon, this extraordinary disease is spreading in Boston and its vicinity. It takes admirably with a certain class of minds, and gentlemen who were esteemed for their sound discretion, heretofore, discover at once to their friends that a screw is loose in the mental machinery.*

Boston M. & S. J., *March 10, 1852*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PROGRESS IN THE LABORATORY-APPROVAL PROGRAM

A pamphlet entitled "List of Massachusetts Laboratories Holding Certificates of Approval from the Massachusetts Department of Public Health" has been published. This list includes 148 hospital, private and public-health laboratories holding certificates from August, 1951, to August, 1952, in designated bacteriologic and serologic procedures. In addition, 44 laboratories are listed as holding certificates in environmental-sanitation procedures. Seventeen of the laboratories hold certification in both environmental sanitation and bacteriologic and serologic procedures.

The laboratory-approval program is the outgrowth of a recommendation in 1936 by a special commission for the study of public-health laws and policies in Massachusetts. This commission noted the varying quality of performance among the laboratories of the State, a matter that had been a problem for some years. As eventually passed in 1939, the law provided for voluntary participation by laboratories in an evaluation program sponsored by the Massachusetts Department of Public Health.

The program started during that year; nearly 125 laboratories were enrolled. Since some of these were obliged to withdraw during World War II because of lack of personnel, the first published list (1946) named only 100 laboratories.

The need for a program of this kind was early disclosed by the fact that even the best laboratories were unable to qualify for certification for all the tests that they desired. Visits were made to these laboratories to assist them in obtaining the necessary additional equipment and in overcoming technical deficiencies.

By the end of the war the program was well on its way, and many laboratories had been able to expand the list of the tests for which they were certified.

In 1939 the Department found comparatively few hospital laboratories in which any bacteriologic tests were made, beyond the examination of stained smears. As recently as 1946 the approvals for the smear examinations for acid-fast bacilli and organisms resembling gonococci made up 32 per cent of the listed approved tests. This year they comprise only 24 per cent of the total tests approved. In 1946, 6 laboratories were approved for isolation of tubercle bacilli from clinical material, as contrasted with 32 laboratories six years later. These and the additional figures in the table show the increasing number of cultural procedures undertaken.

This sixth annual published List of Approved Laboratories may be obtained by any physician by writing to the Diagnostic Laboratory, 281 South Street, Jamaica Plain 30.

HELEN H. GILLETTE
Diagnostic Laboratory
Institute of Laboratories

Comparison of Number of Laboratories Approved for Certain Tests in 1946 and in 1951.

TEST	NO. OF LABORATORIES APPROVED IN 1946	NO. OF LABORATORIES APPROVED IN 1951
Agglutinations	15	44
Blood grouping, Rh testing and cross matching	Evaluation began in 1947	112
Diphtheria cultures	42	76
Hemolytic streptococcus	52	75
Enteric pathogens	9	20
Gonococcus smears	81	113
Tuberculosis smears	90	119
Isolation of tubercle bacilli	6	32
Agents of meningitis	38	50
Diagnostic tests for syphilis	23	37
Malaria	40	68*

*Interest in diagnosis of malaria has been further stimulated by the return of military personnel from Korea.

CONSERVATION OF IMMUNE SERUM GLOBULIN

The Department's supply of immune serum globulin was quickly exhausted as a result of the high prevalence of measles in December, and but for the generosity of the American National Red Cross, physicians in the state would have been obliged for over a month to buy this material, which retails at about $6.00 per vial. Although the Red Cross responded generously, its supply is not inexhaustible; consequently it is hoped that all physicians will co-operate to conserve this important biologic product.

The indiscriminate use of gamma globulin in a large number of children each year to induce a temporary passive immunity will result in pyramiding the number of susceptible subjects in the state and will set the stage for an enormous epidemic of measles. Better public-health management would be to allow healthy children to have measles and thus become immune, since present-day chemotherapy has so reduced the danger of complications.

It must be borne in mind that since only 4 2-cc. vials can be obtained from a pint of blood, it would require a much better blood-donation rate than the present one to maintain a free supply of globulin. Globulin should therefore be reserved for exposed children under six months of age whose mother has not had measles and for exposed children six months to three years of age. This is the most dangerous age and prevention is definitely recommended. Modification should be the aim in children over three years of age except in debilitated or ill children or in children's institutions or hospital wards.

Measles in a healthy child nearly always confers lifelong immunity, and a child can better afford to lose two weeks than can a college student or wage earner. Small doses to secure modification should be carefully calculated, as in a survey of experience in Massachusetts it was found that efforts at modification often led to complete prevention. In such cases the patient acquires no immunity and must start anew when measles again becomes prevalent.

Gamma globulin should not be used in other diseases in which its effectiveness is uncertain.

CORRESPONDENCE

HYPERTROPHY AND HYPERTENSION

To the Editor: I have read with interest the paper by Connolly and Littmann, "Coronary Arteriosclerosis and Myocardial Hypertrophy," that was published in the *Journal* of November 15, 1951. It is not clear in my mind how hypertension as a causative factor of the hypertrophy observed has been excluded. I am aware of many cases in which patients without valvular disease, and so forth, enter the hospital with normal or subnormal tensions and enlarged hearts. In my experience, however, wherever careful investigation was possible previous elevations of blood pressure had been noted. I have assumed, therefore, that hypertrophy in the absence of other documented causes was evidence of preexisting hypertension.

LEO WADE, M.D.
New York, New York

Dr. Littmann offers the following reply to Dr. Wade's letter:

Dr. Wade's attitude concerning this combination is one that is commonly held by internists and pathologists alike. We have thought for some time that hypertension need not be present for the development of hypertrophy, especially since there are adequate physiologic reasons for this phenomenon, purely on the basis of injury. Witness, for example, the hypertrophy that follows inflammatory myocarditis in some cases — or that which has been produced in animals by burning the myocardium.

In clinical medicine, of course, it is almost impossible to rule out the presence of prior hypertension. On the other hand,

where hypertension was once present but subsequently was relieved, as with successful sympathectomy, myocardial hypertrophy diminishes or disappears. We think it likely, therefore, that in our cases, many of which have been followed for years and in which no hypertension was observed during this period, it was not considered a predisposing factor. Additionally, every effort was made to elicit a history of hypertension before these patients came under our observation.

DAVID LITTMANN, M.D.

West Roxbury, Massachusetts

NONCLINICAL NOTES

In the foreword of his latest detective story, *The Case of the Angry Mourner*, Erle Stanley Gardner lauds Dr. Richard Ford, acting head of the School of Legal Medicine of Harvard Medical School and Medical Examiner of Suffolk County (Boston), Massachusetts. Mr. Gardner was so impressed by Dr. Ford's outstanding work that he felt compelled to write this tribute. In a previous book, *The Case of the One-Eyed Witness*, tribute was paid to the department and its previous heads (Editorial. *New Eng. J. Med.* **245**:747, 1951).

Dr. William C. Moloney, clinical professor of medicine at Tufts College Medical School and assistant director of the first and third (Tufts) medical services at Boston City Hospital, will leave on April 1 for Hiroshima, Japan.

Dr. Moloney will serve for the next two years as internist with field units of the Atomic Bomb Casualty Commission, which are engaged in the study of the effects of atomic radiation in Hiroshima and Nagasaki. This work is under the direction of the National Research Council and the National Academy of Sciences.

NOTICES

HARVARD MEDICAL SOCIETY

The Harvard Medical Society will hold a meeting at 8 p.m. on Tuesday evening, March 11, in Amphitheatre D, of Harvard Medical School, at 8 p.m., under the auspices of the Department of Pharmacology.

Dr. Otto Krayer will preside.

The program will consist of papers on "The Normal Rate of Secretion of the Thyroid Hormone in Man," by Dr. Douglas S. Riggs; "The Mechanism of the Oliguria Following Hypotension Induced by Protoveratrine," by Dr. Edward Meilman; "Steroid Piperidine Derivatives Related to the Veratrum Alkaloids," by Dr. Frederick C. Uhle; and "Antagonists to the Cardio-Accelerator Action of the Sympathomimetic Amines," by Dr. Otto Krayer.

SPRINGFIELD ACADEMY OF MEDICINE

The Springfield Academy of Medicine will hold its monthly meeting on March 11. Davis Bosworth of New York City will speak on "Differential Diagnosis of Low-Back Pain."

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

The sixth Annual Meeting of the American Electroencephalographic Society will be held at the Hotel Claridge, Atlantic City, New Jersey, on Saturday and Sunday, May 10 and 11. The council will meet Friday; the scientific meeting will be held on Saturday. The subscription dinner on Saturday evening will be informal and will be open to wives and guests of members. The symposium will be held on Sunday, May 11, from 10 a.m. to 1 p.m.

AMERICAN COLLEGE OF ALLERGISTS

The eighth annual meeting of the American College of Allergists will be held at the William Penn Hotel in Pittsburgh, Pennsylvania, on April 7, 8 and 9. In addition to 20 addresses on general topics and special scientific investigations, there will be luncheon round tables and sectional meetings devoted exclusively to the psychosomatic aspects of the allergic patient, allergy in infants and children and allergic manifestations in the skin, as well as those of the eye, ear, nose and throat. Further information may be obtained from the College, LaSalle Medical Building, Minneapolis 2, Minnesota.

PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH

A program of clinical traineeships in the prevention, diagnosis and treatment of arthritis and the metabolic diseases has been established at the National Institute of Arthritis and Metabolic Diseases by the Surgeon General of the Public Health Service. The purpose of the first group of awards is to improve the competence of physicians in the treatment and rehabilitation of arthritis patients.

Applicants must not be over forty years of age and must be American citizens; they must be graduates of an approved medical school and must have completed a one-year internship in an approved hospital. The stipend for trainees without dependents is $3000 per year; for those with dependents it is $3600. Trainees are placed in qualified institutions of their choice.

Additional information and application forms may be obtained by writing to: Chief, Extramural Programs, National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Maryland.

AMERICAN PSYCHOSOMATIC SOCIETY

The ninth annual meeting of the American Psychosomatic Society will be held at the Hotel Drake, Chicago, on Saturday and Sunday, March 29 and 30. Four scientific sessions will be held, including panel discussions. Further information may be obtained from the society, at 551 Madison Avenue, New York 22, N. Y.

SOCIETY MEETINGS AND CONFERENCES

MARCH 3–APRIL 30. Seventh Postgraduate Lecture Course. Page 274, issue of February 14.

MARCH 8–29. Springfield Hospital. Page 316, issue of February 21.

MARCH 10–13. New Orleans Graduate Medical Assembly. Page 956, issue of December 13.

MARCH 11. Harvard Medical Society. Notice above.

MARCH 11. Springfield Academy of Medicine. Notice above.

MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.

MARCH 12. Rehabilitation Conference. Page 354, issue of February 28.

MARCH 12–26. Lahey Clinic Fellowship Teaching Program. Page 160, issue of January 24.

MARCH 13. Sinusitis. Dr. Francis L. Weille. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

MARCH 13 AND 14. International College of Surgeons. Page 354, issue of February 28.

MARCH 13 AND 27. Alcoholism Staff Conference. Quincy City Hospital. 1:30–3:00 p.m.

MARCH 23, 28 AND 29. Massachusetts Association of Medical Technologists, Inc. Page 354, issue of February 28.

MARCH 24. Annual Lecture of Sigma (Temple) Chapter of Phi Delta Epsilon Fraternity. Page 316, issue of February 21.

MARCH 24–27. American Academy of General Practice. Page 354, issue of February 28.

MARCH 24–28. American College of Chest Physicians. Page 160, issue of January 24.

MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

MARCH 26. Boston Gastroenterological Society. Page 354, issue of February 28.

MARCH 29 AND 30. American Psychosomatic Society. Notice above.

MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

APRIL 2. Tufts Medical Alumni Association. Page 354, issue of February 28.

APRIL 5 AND MAY 3. New England Society of Anesthesiologists Postgraduate Education Course. Page 996, issue of December 20.

APRIL 7–9. American College of Allergists. Notice above.

APRIL 14–25. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

APRIL 17–19. Boston Lying-in Hospital Postgraduate Course in Obstetrics and Pediatrics. Page 315, issue of February 21.

APRIL 21–25. Cancer Seminar. Page 114, issue of January 17.

APRIL 23. Massachusetts Academy of General Practice. Springfield.

APRIL 23. New England Obstetrical and Gynecological Society (Spring Meeting). Hartford, Connecticut.

(Notices concluded on page xix)